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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

GENERAL AND PLASTIC SURGERY DEVICES PANEL

MEDICAL DEVICES ADVISORY COMMITTEE

OPEN SESSION

Wednesday, June 16, 1999

10:00 a.m.

Gaithersburg Hilton
Salons D and E
620 Perry Parkway
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

PARTICIPANTS

Thomas V. Whalen, M.D., Acting Chairperson
David Krause, Ph.D., Executive Secretary

VOTING MEMBERS

Phyllis Chang, M.D.
Benjamin O. Anderson, M.D.
Susan Galandiuk, M.D.
David L. DeMets, Ph.D.

DEPUTIZED VOTING MEMBERS

Thomas B. Ferguson, M.D.
Blake Hannaford, Ph.D.
Michael D. Crittenden, M.D.
Mark A. Talamini, M.D.
Nancy N. Dubler, LLB.
Cedric F. Walker, Ph.D., PE

NONVOTING MEMBERS

Maxine F. Brinkman, RN, Consumer Representative
James W. Burns, Ph.D., Industry Representative

C O N T E N T S

P R O C E E D I N G S

Conflict of Interest and Opening Remarks

DR. KRAUSE: I would like to get the meeting started, please. Good morning, everyone. We are ready to begin this meeting of the General and Plastic Surgery Devices Panel. My name is David Krause. I am the executive secretary of the panel. I am also a reviewer in the Plastic and Reconstructive Surgery Branch in the DGRD.

I would like to remind everyone that you are requested to sign in on the attendance sheets, which are outside the door, on the tables. You may also pick up an agenda, a panel meeting roster and information about today's meeting there. The information includes how to find out about future meeting dates through the advisory panel phone line and how to obtain meeting minutes or transcripts.

Before I turn the meeting over to Dr. Whalen I am required to read a number of statements into the record. I have three statements to read. One is the deputization of temporary voting members. The second is deputization of acting chair, and the third is the conflict of interest statement.

This is the temporary voting status: Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27th, 1990, as amended on April 20th, 1995 and October 10th, 1997, I appoint the

following people as voting members of the General and Plastic Surgery Devices Panel for this meeting on June 16, 1999: Blake N. Hannaford, Nancy A. Dubler, Mark A. Talamini, Cedric F. Walker, Thomas B. Ferguson and Michael D. Crittenden.

For the record, these people are special government employees and are consultants to the Center for Devices and Radiological Health under the Medical Devices Advisory Committee. They have undergone customary conflict of interest review. They have reviewed the material to be considered to this meeting. And, it is signed by Dr. Elizabeth Jacobson, Acting Director, Center for Devices.

I would now like to read the appointment of the temporary panel chair person. I appoint Thomas V. Whalen, M.D. to act as temporary chairperson for the duration of the General and Plastic Surgery Devices Panel meeting on June 16th, 1999. For the record, Dr. Whalen is a special government employee and is a voting member of the General and Plastic Surgery Devices Panel. Dr. Whalen has undergone customary conflict of interest review. He has reviewed the issues to be considered at this meeting. It is signed by Dr. Feigel who is the present Director of the Center for Devices.

Finally, I would like to read the conflict of interest statement. The following announcement addresses

conflict of interest issues associated with this meeting, and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the panel participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

The agency took into consideration matters regarding Drs. Cedric Walker, Blake Hannaford, Susan Galandiuk and Benjamin Anderson. These individuals reported financial interests in firms at issue, but in matters not related to the topic to be discussed by the panel. The agency has determined, therefore, that they may participate fully in today's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in

the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

At this time, I would like to turn the meeting over to Dr. Whalen.

Panel Introduction

DR. WHALEN: Thank you, Dr. Krause. My name is Thomas V. Whalen, and I am head of the Division of Pediatrics Surgery at Robert Wood Johnson Medical School at Camden, where I also hold the role of Associate Professor of Surgery and Pediatrics.

Today, our panel will be making recommendations to the Food and Drug Administration on a premarket approval application. Our next item of business is to introduce our panel members, who are giving of their time to help the FDA in these matters, and the FDA staff who are here at this table. I would like to ask that each person introduce him or herself, stating his or her specialty, position title, institution and his or her status on the panel as voting member, industry or consumer representative or deputized voting member. I would like to ask Dr. Burns to begin and we will go around the table.

DR. BURNS: I am Jim Burns. I am Vice President of Biomaterial and Surgical Products Research at Genzyme

Corporation, and I have a Ph.D. in bioengineering, and my expertise is in biomaterial science.

MS. BRINKMAN: I am Maxine Brinkman, Director of Women's Services, from Mercy Medical Center in Mason City, Iowa. I have an RN and a masters in public health.

DR. WHALEN: Could you each mention your status on the panel?

DR. BURNS: I am the industry rep. for this panel.

MS. BRINKMAN: I am the consumer rep.

DR. DEMETS: My name is David DeMets. I am a biostatistician, University of Wisconsin, and I am a voting member of the panel.

DR. FERGUSON: I am Tom Ferguson, Cardiothoracic Surgery, Washington University School of Medicine. I am a deputized voting member.

DR. HANNAFORD: My name is Blake Hannaford. I have no middle name, which is what the "N" stands for I think --

[Laughter]

I am a Professor of Electrical Engineering at the University of Washington, in Seattle. I am also Adjunct Professor of Bioengineering and Adjunct Professor of Surgery, and I have a Ph.D. in electrical engineering and computer science. I am a deputized voting member of the panel.

DR. GALANDIUK: Susan Galandiuk. I am a colorectal surgeon and I am an Associate Professor of Surgery at the University of Louisville, and I am a voting member of the panel.

DR. CRITTENDEN: I am Mike Crittenden. I am a cardiothoracic surgeon at the West Roxbury VA, and affiliated with the Harvard Medical School. I am a deputized voting member.

DR. ANDERSON: I am Ben Anderson. I am an Associate Professor of Surgical Oncology at the University of Washington, in Seattle. I am the Medical Director of the Breast Care Program there, and a member of the Fred Hutchinson Cancer Research Center.

DR. CHANG: I am Phyllis Chang. I am an Associate Professor in the Department of Surgery, Section of Plastic Surgery, with a joint appointment in the Department of Orthopedics Surgery for Hand and Microsurgery, in the University of Iowa, College of Medicine. I am a voting member.

DR. TALAMINI: Mark Talamini. I am an Associate Professor at Johns Hopkins University School of Medicine. I am a general surgeon, gastrointestinal surgeon primarily, and Director of Minimally Invasive Surgery at Hopkins, and I am a deputized voting member.

MS. DUBLER: I am Nancy Dubler. I am Director of

the Division of Bioethics at Montefiore Medical Center, and a Professor of Bioethics at the Albert Einstein College of Medicine, and I am a deputized voting member.

DR. WALKER: Cedric Walker, Professor of Biomedical Engineering at Tulane University, in New Orleans. I am a deputized voting member.

DR. WITTEN: Celia Witten, Division Director of DGRD in ODE in CDRH and FDA. I am a representative of FDA, not a panel member.

DR. WHALEN: Thank you. I would like to note for the record that the voting members present constitute a quorum, as required by 21 CFR, Part 14.

Next, we are going to hear from Mr. Stephen Rhodes who will give the panel an update since our last meeting in November. Mr. Rhodes?

Update Since the Last Meeting

MR. RHODES: Thank you. I am Stephen Rhodes. I am the Branch Chief of the Plastic and Reconstructive Surgery Devices Branch. In November the panel made recommendations on the classification of five wound dressings, gauze, hydrophilic wound dressings, hydrogel wound dressings, occlusive wound dressings and porcine wound dressings.

The FDA is working on a final rule classifying four of those wound dressings, the gauze, the hydrogel wound

dressings, the occlusive wound dressings and the hydrophilic wound dressings, as Class I exempt devices. These are products that do not have any drugs, any biologics or any animal source materials in them. We are still working on classifying the porcine wound dressings. We appreciate your assistance in helping us to classify these products, and we are pleased that we are reaching closure on classifying all these important classes of products.

Other activities in the branch -- we have completed a guidance document on surgical meshes. We are working on updating several guidance documents, a guidance document for breast implants which was developed in 1995, and we are also updating the guidance documents for interactive wound dressings and noninteractive wound dressings. We are also developing a new guidance document for sutures. Lastly, we are working on a final rule, calling for PMAs for safety and efficacy data for saline-filled breast implants for mammary prostheses. We are expecting that that final rule will be published this year, and we are looking forward to the panel's participation in the discussion of those PMAs in the future.

That concludes my update. Thank you.

DR. WHALEN: Thank you, Mr. Rhodes. We will next hear from Mr. Larry Kessler regarding postmarket evaluation at FDA's Center for Devices and Radiological Health. Mr.

Kessler?

"Postmarket Evaluation at FDA's Center for Devices and Radiological Health"

MR. KESSLER: Good morning. My name is Larry Kessler. I am the Director of the Division of Surveillance and Biometrics at FDA. I am not a voting member..

[Slide]

Around two years ago, maybe a little less, Dr. Susan Alpert, who is the Director of the Office of Device Evaluation, asked me to give a brief presentation to a group of the panel chairs who collected together to review issues and common to panels. And, I talked a little bit about postmarket evaluations at FDA and a number of the panel chairs asked me to come, give presentations to the members of the panels, not just the chairs.

So, Dr. Tom Gross, who is the head of my Division of Postmarket Surveillance, and myself have been going around this year to give presentations to all the panels, trying to give you a little flavor for how we work on the postmarket side. So, in 15 minutes I am going to describe everything we think you need to know, in a brief primer, on postmarket evaluation.

As I am going to show you in a minute, there are a variety of different mechanisms which use similar names and may sometimes get confusing to you, as panel members, and

are even sometimes confusing to FDA staff who work with them on a week to week basis.

[Slide]

I am going to describe a few of the methods of device postmarket evaluation at the Center. I am going to present the challenges we face in accomplishing postmarket evaluation roles, and just try and describe the pivotal role that you, as the advisory panel, can plan in helping us accomplish the goals for making sure that devices are safety and efficacy, not only as they reach market but as they spend time on the market.

As you well are aware, most of the time a device is in use is postmarket, not premarket, and that is the bulk of our concern. I believe you have handouts on this in case you want to take notes, and I hope you have questions.

[Slide]

This is a brief schematic of how we view the world. This is the world of the Center for Devices viewed from the context of the Office of Surveillance and Biometrics.

For the most part, from design through clinical testing the bulk of this work, the best majority of this is done by manufacturers, clinicians, their patients and not by the FDA. This is where the bulk of the work is done in the premarket phase. FDA gets increasingly involved as any

device or modification of a device goes through lab and bench testing and clinical testing. Once it reaches FDA review, we have the clinical community that we hope we are interacting with a lot. The advisory panels are one mechanism for that. Once a device is cleared for market, we have a variety of tools that we can use in the postmarket period to evaluate continued safety and effectiveness issues during the postmarket period.

I am going to talk quite a bit about the medical device reporting program, and then about postmarket surveillance authorities and postapproval studies. You are probably most familiar with postapproval studies but I will try and talk about all three and weave them together a little bit. I am not going to talk very much about our epidemiology program or field inspection program, which are also important components of postmarket evaluation but I don't have that much time today and I can always come back if you are interested.

[Slide]

What do we care about in the postmarket period? Clearly, long-term safety is one issue that matters to us, matters to you, matters to everybody involved. We are also very interested in the postmarket period about looking at performance of a device in community practice. You will see premarket applications that frequently come from well-

controlled studies, clinical settings where there may be device experts; there is a great deal of attention to protocol. Once devices get out into the community they don't achieve the same level of performance often, and sometimes you see problems you would not have seen.

In a minute I will tell you a little bit about the MDR program, but if you think you can imagine everything that can happen to devices you clear, you can't. You must see these reports. It is amazing what people would think about doing when devices have been approved and cleared for market.

Effects of change in user setting -- as you well know, an enormous amount of product has left the hospital walls and moved to the bedside, and it has been particularly true over the last 16 years since the imposition of DRGs by HCFA and the insurance world. People are trying to move patients out of hospitals faster and faster.

Some of this is very positive from a therapeutic standpoint, but it means increasingly sophisticated technologies making it to the bedside. We, on the postmarket end, tend to see an increase in the different kinds of problems that we see. This includes serious injuries and deaths from a variety of products that you would not tend to see in a hospital setting but you will see in a home at bedside because you have people who are less

expert and who don't have the resources to deal with problems once they arise. So, whether in fact some piece of technology should move from the hospital to the bedside is something that we will often ask in the postmarket of a product.

[Slide]

One of our most quoted and used mechanisms for looking at product problems is the Medical Device Reporting Program. Manufacturers must by law report deaths and serious injuries, if a medical device may have caused or contributed to the event, as well as malfunctions. Now, in the European Union these are called "near incidents." A product that fails that did not happen to cause a death or serious injury but could if it occurred without such fortuitous circumstances is a mandated reportable event by a manufacturer.

Since the Safe Medical Devices Act of 1990, all user facility in this country -- all hospitals, all nursing homes, ambulances, surgical care centers, they are supposed to also report all deaths to the FDA, and all deaths and serious injuries to manufacturers of devices if they know the manufacturer of a product.

We get roughly 95 percent of our 80,000 reports from manufacturers and less than 5 percent come from hospitals, nursing homes, etc., and most of the events we

get from manufacturers are happening in hospitals, nursing homes, etc. So, we get the reports from manufacturers. Many of the manufacturers you see here stand up before you are critical components of our ability to monitor postmarket data. Hospitals and nursing homes -- some of them do well and many do not.

[Slide]

Beginning in about 1992, we were receiving at FDA over 100,000 medical device adverse events a year. We were really swamped with work. It was really a challenge because we had roughly 15 analysts to look over 100,000 reports and it was really a daunting task.

Information in these reports is supposed to include device specifics, event description, event date, patient characteristics, etc., but these reports often have limited information. Sometimes a manufacturer will come to us and they will say, "I'm going to send you a report but it's not complete." By law, they are supposed to complete all the information they can get. We will ask them why not. They will call the hospital who will tell them, "my lawyer tells me not to tell you what really happened." I am sorry for the legal guys out there; it's just something that happens in the walls of the hospital, and it sometimes is a challenge for us.

But often the reports are very useful and we use

them to prompt a lot of actions. What I have done is select a couple of products that are relevant to this panel where we have taken some actions based on the data from the MDR program. For example, we get reports of operating room fires with ESUs frequently. It is a common problem. You may have seen a piece that I think "20/20" did about a year ago, and it is something that we see repeatedly, and we think it is a problem that can be reduced by more Public Health action and we proposed to take some actions this year to make clinicians and the public aware of how we can reduce fires related to ESUs.

More recently, in 1997, a product was approved by FDA, I believe through the 510(k) program, for a collagen impregnated synthetic sling. We noticed some increased reports in 1998 and conducted several inspections with the manufacturer who eventually, upon more careful examination of their complaint data and our MDR reports, decided to recall the product in January of this year, and they will no longer market or manufacture the device.

DR. TALAMINI: Excuse me, sir --

MR. KESSLER: Yes?

DR. TALAMINI: -- as a surgeon, I have to know what an ESU is.

MR. KESSLER: Electrosurgical cautery unit.

DR. TALAMINI: Sorry.

MR. KESSLER: We are talking about things that are used in a very rich oxygen environment around drapes.

Based on the MDR system, we will also conduct directed inspection of facilities, and we will also conduct postmarket studies. We did one on polyurethane foam-coated breast implants a few years ago -- successful.

[Slide]

I am going to spend a couple of minutes on these two authorities because these two will probably interest you more than anything else. The Safe Medical Devices Act passed Section 522 postmarket surveillance. We have had this authority for about nine years now. We also are allowed to call for postapproval studies under the PMA. Both of these are mandated by law. Postapproval refers to PMA products only, whereas, Section 522 covers, as modified by FDA in May, 1997, Class II or III products whose failure may present a public health problem. I have stated that quite generally; the statutory language is a little more specific.

We have two mechanisms at FDA for calling for or requiring manufacturers to conduct studies in the postmarket period. These are principally done for safety concerns. They don't have to be done only for safety concerns; we can ask effectiveness questions but the principal spirit of the postapproval and postmarket and studies is for safety issues

but there are effectiveness and performance questions which are sometimes asked as well, and sometimes they are not separable for a certain kinds of device; its safety is its effectiveness issue. We see both authorities as complementary to postmarket.

[Slide]

To call for a study, we need to figure out what are the criteria to ask for such a study because studies in the postmarket period are quite challenging, and I will explain that in a minute. First of all, we need to understand the critical public health question, and these postmarket study requests can either occur from "for cause" situations or new expanded conditions of use or an evolution of technology.

We have to consider before we actually require a postapproval or postmarket study other mechanisms we might use to collect the same relevant data. This could include the Medical Device Reporting Program, secondary database analysis of, say, the HCFA data that we have in house, etc.

I want to talk for a bit about practicality and feasibility on my next slide and, most importantly, how will the data be used? Before we ask for a postmarket study, we need to figure out what we are going to do with it. Are we going to modify the label? Are we going to ask for a recall? Change the way we approve a device? What about

communication to the public, health professionals, etc?

[Slide]

There is a wide variety of study approaches that we should use in the postmarket period. With the institution of required or discretionary postmarket surveillance after SMDA, FDA tended to use a fairly heavy approach to postmarket studies and asked for things at the bottom end of this list. We were asking for randomized, case control or well-documented trials, and we had a lot of problems getting those accomplished.

With the recent FDAMA, the clear signal from Congress was to expand the kinds of things we might allow manufacturers to do to provide valuable postmarket data. So, in our recent Federal Register notices about our postmarket program we have expanded the kinds of designs that we might ask for not only from detailed randomized studies, but also possibly something as simple as detailed review of complaint history in files of manufacturers or literature, as well as non-clinical testing of devices.

[Slide]

But postmarket challenges have been very frustrating. They are frustrating for at least these four reasons: First, rapid evolution of technology make the studies that we are doing sometimes obsolete. By the time we get a protocol in house, the manufacturer goes and asks

clinicians for data, they begin to collect data, they are already on the second or third generation of that product and it is questionable of what utility the postmarket study might be.

It is not true of all medical device products but it is true of some. I still remember -- I spent, I guess, ten years at the National Cancer Institute working in cancer prevention and control, and when I arrived in 1984 one of the first things I was told there is, "the Pap smear is about to become obsolete, guys. It's been used for thirty years and we have much greater technology that's coming down the road, and it's going to be all gone by the time you hit 1990." As you all know, it is still one of our major tools for cancer prevention and detection. It is true for devices. We hear things are going to be obsolete but you would be surprised at how long they hang on.

There is a lack of incentives for industry. The plain fact of this is when we ask industry for postmarket studies, it is generally not good news and their interest in helping us with those data is relatively minimal. It is unlikely that the end of the postmarket market study is going to be "what a wonderful product." It is more likely to be "we've discovered some problem and we want to tell you about them." Although this may be good marketing in the long-run, for industry it is not exciting news generally.

So, they are generally reluctant. Some of them have dragged their heels on some of the postmarket studies we have asked them for.

There is a general lack of interest in the clinical community. Those of you at Hopkins and the Fred Hutch and Washington U don't make a lot of publications off products that are already marketed, but it is nice to have sexy new technology for which you can help get information out in the literature. So, getting the clinical community interested in postmarket studies has been a frustrating challenge not only for us but also for industry. They find it hard.

Finally, sometimes on both ends, industry and the FDA end and on the advisory panel end, we have not clearly specified the public health question of importance for which to conduct a postmarket study.

[Slide]

That is the challenge I will leave you with. When considering postmarket studies, whether postapproval or 522 -- and FDA can figure out the right mechanism to use; they each have different strengths and weaknesses. Postmarket studies under 522 can be done for 510(k) products. Condition of approval only apply to PMA products. We need to ensure that this is of primary importance, that it is not a secondary question. I reviewed, in 1997/8, almost a dozen

panel recommendations for postapproval studies or for PMA products. For half of them a postapproval study was asked for, and in most of those I could not detect clearly specified the question the panel was asking for us to ask a manufacturer, and that is a real challenge for us. So, if you are going to ask for a study, you really need to specify what you are trying to answer. That is critical.

Try and figure out what the clinical or regulatory relevance is for the question. What are you going to do with the data? Are you going to suggest we change the label? Are you going to suggest we put out a public health advisory to the clinical community, the lay community, hospitals? Who is going to get this information? Will we conduct a recall? If you discover, say, a long-term safety problem that was above some threshold, tell us the issue that you are interested in; clearly specify the question that will help us specify the question and work with the company to develop a design that makes sense. If you can do that, you can help us a lot.

[Slide]

Finally, I hope the future of the Medical Device Reporting program and postmarket surveillance -- I haven't talked a lot about the future of MRD, it is less relevant here -- we are trying to use a wider variety of design approaches to give the industry more flexibility and us more

flexibility to answer the right question correctly. We work in collaboration with the industry and the clinical community, and we are trying to obtain expanded access to different data sources, including registries, and we are beginning to hold a variety of workshops and conferences with industry and with the academic community to get better data in the postmarket period. Our data are somewhat limited, but with better specified questions, better specified studies and increased access to wider data sources which exist in the public domain we think we can answer the questions that we need to fill our mission in monitoring postmarket safety and effectiveness of devices.

Thank you for your time. I will take questions if you have any.

DR. CRITTENDEN: I have two questions. Could you talk about off-label use, and the second question is, there seem to be 100,000 adverse events per year and I just want to know how close that is to what the estimates are in terms of the actual number.

MR. KESSLER: I will answer the second question first because it is easy. We have lousy estimates -- let me go to the first question and then I will come back because the second one I have a longer answer for. Off-label use -- we don't explicitly track off-label use in terms of studies unless you or we suggest what we should look for. However,

that is one of the great things about the Medical Device Reporting program.

We get routinely evidence of off-label use, and I will give you a great example -- it is not so much relevant for this panel, although I am sure we have dozens of them for you. It is an example I presented to the panel chairs. Soon after coronary stents were developed and started to be used, we would get reports of deaths or serious injuries related, and one of the egregious uses of stents is one clinician, wanting to keep a large part of an artery patent used 27 stents stringed in a row. They were labeled single stent only. Stringing a few of them together was something some clinicians were starting to do but one clinician got carried away, let's say, and the patient did pass away. The patient may have passed away anyway; it may not have been directly related to the use. But the MDR system is rife with those examples, and those are some of the ones on which we act. We will see a use that was not intended by the manufacturer which will provoke death or serious injury, and we will use public health advisories and safety alerts to the clinical community to tell them what we think is going on. So, that is the answer to the first question.

The second answer, the General Accounting Office made an estimate about a decade or so ago that we get about one percent of the real events that are happening. So, if

we get 100,000 events there are a million, and I think that estimate could be plus or minus, another factor of five or ten, quite frankly. It could be way up or way down. It is not very good. We have lousy denominator data, and even if we ask manufacturers to supply it, which we were going to do in 1996 but have walked away from it for a variety of reasons, it is not clear we would get good numerator data. You need both.

[Slide]

So, Congress, in its wisdom, supported the FDA by providing the legislative mandate for FDA to begin conducting a sentinel or device surveillance network program. We did a pilot study two years ago, which just ended last year, where we used 24 facilities and concentrated on those facilities in getting them to report faithfully, and we can get much better tracking of what is going on. The new sentinel system is supposed to begin in the next year or two, depending on the appropriations. We have been directed in statute to develop a sample user facility system so we can have a lab where we can look at good estimates of adverse events and denominator uses. Right now we don't have that. That is where we are going, and you will be hearing more and more about this system over the years provided Congress can find the wherewithal to appropriate the funds. But that is the way we need to go.

It is a really exciting program for us, and we think it is going to make a big difference in being able to find out how devices are really used.

DR. CRITTENDEN: Thank you. You have partially answered my question, but if you had all the data you wanted do you have the resources to really evaluate it properly at this stage?

MR. KESSLER: If we got 100 times the reports? No, no. If we got all the reports I wouldn't need to. I will just tell you about something we have done in the past two years, and give you a flavor for how we can work around this. We get 100,000 reports, but many of them are absolutely repetitive. It is the same thing over and over. The best example that relates to you is capsular contracture of breast implants. Once we get the first few hundred of those, the next 20,000 are not very interesting.

Now, I have to say this, and I am glad there is a consumer advocate here, we have a problem convincing women with breast implants and some of their associated legal counsel that more MDR reports of capsular contracture aren't a scientific way to help us evaluate a problem. So, what we have done is to move to a program that we call summary reporting. Once we see a problem over and over, we work with the industry, we work with the advisory panels, we work with the clinical community and try to figure out is there

something to be done. When there isn't we have the wherewithal to either have reports sent in, in a summary fashion so we get, say, one table four times a year of the same kind of complaint and, in that way, you can get a thousand complaints reviewed in a minute. So, that is one avenue we have taken. We can also give an exemption to companies -- don't report that. Keep it in your complaint file and in your quality system reporting and we can handle it there.

But the magic behind the sentinel system is that if we can get a good sample of between 5-10 percent of the hospitals in the country, the way the National Nosocomial Infection Surveillance System does in CDC, you can track the real problems fairly fast and you don't need a 100 percent sample. So, if we can get a good 5 or 10 percent of the hospitals reporting, and the rate in the sentinel pilot was 20 times current report rates, we would get a lot more reports but from a much smaller sample. So, then we could handle it. I have 15 outstanding analysts. Almost all of them are nurses; one is not, but they are fabulous, and they pick up really unusual problems. They find needles in haystacks -- really unusual.

Other questions?

DR. WHALEN: Thank you, Mr. Kessler. Before proceeding to the next listed item on the agenda, for an

important unlisted piece of business I turn the floor back to Dr. Krause.

DR. KRAUSE: Sometimes we have the fun activity of handing out plaques and things. So, Jim?

Presentation of Award

MR. DILLARD: I am Jim Dillard. I am the Deputy Director in the Division of General and Restorative Devices. It is my distinct honor to get to stand up here and recognize one of you, although we would like to recognize all of you, but one of you for the distinct accomplishment of being on this panel now for your requisite period of time, and perhaps it may be this individual's last panel meeting, although this particular individual has been so good for us that usually when we have a particularly good member we keep them around and call them back from time to time, and have them perform their services on a semi-regular basis.

So without further ado, I would like to recognize Dr. James Burns, and your distinct recognition says, "in recognition of distinguished service from the General and Plastic Surgery Panel and Medical Devices Advisory Committee," and it is signed Elizabeth Jacobson, Acting Center Director, and also Jane Haney, Commissioner of the Food and Drug Administration. So with that, Dr. Burns, thank you for all of your service and, hopefully, you will

hang this plaque next to some of those approval orders you get from your own company's products.

[Applause]

I will turn the meeting back to you, Dr. Whalen.

DR. WHALEN: Thank you, Mr. Dillard, and congratulations, Dr. Burns.

We will now proceed with the open public hearing session of the meeting. All persons who wish to address the panel should speak clearly into the microphone as the transcriptionist is dependent on this means of providing an accurate record of this meeting.

We are requesting that all persons making statements during this open public hearing disclose whether or not they have any financial interests in any medical device company. Thus, before making a presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interest, if any, or state that there is none. At the time that the agenda was drafted for this meeting there had been no formal requests made to FDA to present at this particular juncture of the meeting. Since there are no formal requests, I ask now that if there is anyone who wishes to address the panel that they please raise their hand.

Since there are no requests to speak in the open public hearing, we will now proceed to the open committee

discussion. I would like to remind the public observers at this meeting that while this portion of the meeting is open to your observation, public attendees may not participate except at the specific request of the panel. There will be, however, a further opportunity for the public to comment near the end of the meeting. We will now proceed to the sponsor's presentation.

Applicant Presentation, Intuitive Surgical Incorporated

Introduction

MR. DANIEL: Good morning, ladies and gentlemen, members of the panel and FDA. On behalf of Intuitive Surgical, we are pleased to have the opportunity to present today data and information in support of safety and effectiveness for the Intuitive surgical endoscopic instrument control system. My name is Mike Daniel. I am the vice president of regulatory and clinical affairs for the company.

[Slide]

We have with us today our president and CEO, Lonnie Smith; our founder and medical director, Dr. Fred Moll who will provide background for the system and discuss the technology. We have Dr. Guthart here with us today to answer any technical questions. He is the director of systems engineering. We have two of our four investigators. We have our principal investigator, Dr. Barry Gardiner from

Oakland, California, and we have our second U.S. clinical investigator, and that is Dr. Alan White from Tacoma, Washington. Dr. Gardiner will present the bulk of the clinical data today. We also have our statistician, Dr. Dan Bloch from Stanford, and Dr. Bloch will provide a brief statistical overview.

[Slide]

Intuitive Surgical was founded in 1995, with the purpose of developing computer-assisted technology. We have technology licenses from Stanford Research Institute, IBM and MIT. We have approximately 100 full-time employees, half of whom are engineers. We are currently marketing the system in Europe.

[Slide]

A brief summary of the regulatory status -- we obtained clearance from FDA via the 510(k) process in July of '97 for the following indication: Assistance in the accurate control of blunt dissectors, retractors, stabilizers and endoscopes in endoscopic surgical procedures. That would include laparoscopic as well thoracoscopic.

[Slide]

What we are here today to do is for a proposed additional indication, and that is, assistance in the accurate control of graspers, sharp dissectors, needle

holders, and electrocautery and accessories, and we are going to limit this to laparoscopic surgical procedures because that is the data we are presenting.

[Slide]

A quick overview of the regulatory process to date -- we submitted the 510(k) in December of 1996, and we obtained clearance in July of 1997. At about the same time the agency determined that clinical data would be necessary for sharp dissection, electrocautery and, in their minds and our minds conjunctively, surgical procedures as opposed to assistance.

We submitted an IDE and obtained conditional approval in July, 1998, and then proceeded with our clinical study and completed the 30-day follow-up required in December of 1998. We submitted a 510(k) in January of this year and last month FDA made the decision to convert that 510(k) to a PMA.

[Slide]

Clearly, today's objective is to present data in support of that PMA approval.

[Slide]

I would like to introduce now our medical director, Dr. Fred Moll, who will describe the technology.

Technology

DR. MOLL: Good morning. I would like to first

thank the panel for the opportunity to present here today. By way of background, I am an M.D. and received residency training in general surgery. About five years ago I was introduced to the pioneering work of the Stanford Research Institute in the area of computer-assisted surgery. I became convinced that this approach could have a positive impact in minimally invasive technique, and it is this interest that led to the founding of Intuitive Surgical.

Before we present the study results today, I want to take you through a few minutes to introduce Intuitive's technology and the reasons for its development.

[Slide]

First a clarification of terms, computer-assisted surgery can be defined as a technique in which the surgeon's motion is assisted by a computer. How is this technique fundamentally different than conventional surgery? It interrupts the direct mechanical connection between the hand and the instrument, and inserts an electrical interface.

How can it improve existing technique? To explain this I want to discuss the advantages and disadvantages of both open and conventional laparoscopic technique, and suggest how computer-assisted surgery can provide clinical value.

[Slide]

In open surgery a large incision permits full

range of motion of the surgeon's hands and wrists inside the body cavity and close to the target anatomy. The disadvantage of this technique is simply that it requires a large incision.

[Slide]

In contrast, the advantages of conventional laparoscopy over open surgery relate directly to the dramatic reduction in incision size afforded by this technique. Advantages include reduced postoperative pain, shorter recovery, reduced hospital stay and, in many cases, lower health care costs.

[Slide]

However, the disadvantages of conventional laparoscopy relate to the fact that dexterous tasks become more difficult. The surgeon experiences reduced control because his or her hands are outside the body cavity and at the end of long instruments. Also, the body wall constrains movement and freedom of motion is reduced. Thus, control is necessarily transferred from the fingers and wrists to the surgeon's shoulders and elbows. Counter-intuitive motion is also a problem due to the body creating a fulcrum effect. The surgeon is forced to move his hands left to move the instrument tip right. Finally, the loss of eye-hand alignment and depth perception create challenge to good surgical technique.

[Slide]

The great attribute of computer-assisted surgery is that in very specific says it allows enhanced instrument control. This enhancement is accomplished by, first, increasing range of motion by allowing Intuitive control of an articulating wrist inside the body cavity. Second, computer-assisted technique increases control by electronically shortening instruments and eliminating the fulcrum effect. Further precision is enhanced by the addition of motion scaling and tremor reduction. Finally, the Intuitive surgeon console provides 3D vision and eye-hand alignment.

[Slide]

I would like to show a video to illustrate some of these points. First, open surgery.

[Video presentation]

As you see in this video, the surgeon enjoys full range of motion for his or her hands and wrists because of the large incision used in open technique.

In laparoscopy, however, the surgeon's hands are at a significant distance from the tissue holding the end of long instruments. Here he or she is forced to control the instruments with shoulder and elbow movements rather than using the more dexterous movements of the fingers and wrists. In addition, the surgeon operates from a two-

dimensional video that is not in the same visual field as his or her hand movements.

In computer-assisted surgery, as shown here, Intuitive manipulators are able to provide precise motion at the instrument tip. The surgeon, positioned at a console, can control three manipulators with attached articulating tools such that the surgeon directs the tip of the instrument inside the body cavity. This increases range of motion, control and dexterity. In addition, the system console provides 3D vision and eye-hand alignment.

With the addition of motion scaling and tremor reduction, the surgeon's intended movements, at the bottom of the screen, are transmitted precisely to the system's instrument tips, at the top of the screen. The result is enhanced dexterity and precision. In addition, the system provides a means for efficient instrument change and the manipulators are able to remove the system from the operative field very quickly if necessary to do. With computer-assisted technique the instrument tips are afforded a much larger range of motion, provided in a variety of tips for different clinical purposes, and the system has a master that feeds electronically to instrument manipulators. These manipulators articulate at the instrument tip to provide control.

This, again, is the three-dimensional viewer that

provides eye-hand alignment and, as you can see, the motion of my fingers at the bottom of the screen are transmitted very precisely to motions of the instrument tip at the top of the screen.

This is an example of how instruments are changed in the system. If the manipulator needs to be moved quickly out of the surgical field, that is also quite easy.

The Intuitive System is being used clinically in general, gynecologic and cardiac surgery outside the U.S., where it is approved for these indications. As seen in this footage, the enhanced dexterity offered by the system has helped accomplish precise suture placement in procedures such as mitral valve repair, as seen here.

[Slide]

In summary, the Intuitive computer-assisted surgery system enhances instrument control, first, by augmenting freedom of movement via articulating instruments which provide seven degrees of freedom inside the body cavity; second, by transferring hand control to instrument tips, thereby electronically shortening the surgeon's instrument; third, by eliminating counter-intuitive movement; and, fourth, by providing motion scaling, tremor reduction, coaxial eye-hand alignment and three-dimensional imaging.

[Slide]

The net effect is that the system enhances laparoscopic technique by recapturing many of the advantages of open surgery, thus, allowing more dexterous surgery in a minimally invasive format.

Having described the dexterous attributes of the system, it is important to understand that the study that we will present was not designed to quantify dexterity. We do believe that this study gives ample evidence that the Intuitive device is safety and efficacious, and that the enhanced dexterity can be appreciated from the video footage.

[Slide]

I would like now to ask Dr. Dan Bloch to present the statistical analysis of our clinical trial. Dr. Bloch?

Statistical Analysis

DR. BLOCH: I have no financial interest in Intuitive Surgical. I have no stock options. I am being reimbursed for my expenses to attend this meeting, and I do get paid for the hours that I do consult for Intuitive Surgical.

[Slide]

What you are going to hear today are the results of two different studies, two separate studies, each one controlled. The design of the studies was as randomized, controlled clinical trials. The objective for both studies

was to show equivalence.

So, I am going to start by just giving a brief overview of tests of equivalence and how we defined the methods that we used for these two studies. The objective of the equivalence study is to show that the study group is clinically not significantly worse than the control group with respect to predetermined endpoints. Another way of saying this is that the aim is to demonstrate that outcomes of the treatment group and the control group are close enough so that the treatment and control group do not differ in a clinically important way.

What is different with clinical equivalence tests is that one has to define what differing in a clinically important way means. The methods that we employed to determine these parameters for the different endpoints were, first, prior to study we estimate the outcome average for the control group, denoted by the letter C in this slide, and we obtained that from the literature. Then in relation to that average value that we obtain as an estimate from the literature, then in consultation with our expert clinicians we determined the maximum amount that the test group average can attain and still be clinically acceptable, as denoted by T. Then simply the amount that is not considered to be clinically important is defined as either the difference or the ratio of these averages. I have used the Greek symbol

for delta to denote this difference, which statisticians love to use for parameters. Finally, the test of equivalence simply compares the observed data to this parameter delta.

[Slide]

We employed two different types of statistical tests for equivalence. The first is appropriate for success/failure data, yes/no data. For example, in our study the primary outcome for safety is complication. From that data we obtain a proportion for the group, either the treatment group or the control group, and using the published methods Blackwelder we simply take the difference between the two, and that is the delta.

Specifically, as an example, one of the studies has to do with what I will call the lap missing procedure. Dr. Barry Gardiner will explain these in more detail. I will defer questions of clinical meaning to him. I don't feel I am competent to answer those kinds of questions. But as an example, for lap missing study, there, from the literature and our best interpretation of what is right, the complication rate in the control group is estimated to be two percent. The acceptable complication rate for the test group is nine percent, so simply the difference of nine minus two is delta.

What this means is that if the difference between

the treatment and the control group is over seven percent, then we would say that is not clinically acceptable. That is too big to call the two treatment groups equivalent.

[Slide]

For continuous outcomes we use the ratio of the expected group averages rather than the difference. This is based on a method that is published by Dr. Fieller. As an example from the second study, having to do with lap choles, for procedure duration the literature estimate for the amount of time for the surgical procedure was 89 minutes, and the clinically acceptable procedure duration deemed by the clinicians was at least double that, and I have written down 178 minutes here, which is double 89. Here the delta is simply the ratio, 178 divided by 89.

This methodology is in the protocol for continuous outcomes, and it is especially useful when the actual control observations differ from the prior assumptions. Recall that our assumptions having to do with the control means come from the literature, and when we do the experiment it might be quite different from that. We hope we got a good estimate because our estimate of delta depends on it.

But, as an example, procedure duration for the lap chole control arm was 69 minutes. That actually was the average, quite different from 89 minutes. The ratio is

especially useful when such a situation occurs, that is, the ratio of two still makes sense in this case.

[Slide]

Some of the delta values in the tables were incorrectly specified. In what follows I will try to present a fair and balanced presentation of the assumptions and try to clearly indicate that the deltas were predetermined. There was a disconnect between the text and the tables. Unfortunately, I did not have an opportunity to review the tables and text before the protocol was submitted to the FDA, and did not discover the discrepancies until later, however, upon careful reading of the protocol as a whole, I think it is quite clear what our intent is and this is what I wish to review now in the next slides.

Regarding the next two bullets, as I have already indicated, sometimes the control averages were quite different that we saw in this study results and that does have a bearing on the actual test of statistical equivalence. We will see that later. Finally, the testing of equivalence methods that I have described are not valid if we have low outcomes, low average outcomes and we will see that for conversions and complications, in fact, we have no outcomes and you can't then estimate the standard error.

[Slide]

Again, I just want to defer to Dr. Gardiner any

clinical interpretations regarding the outcomes that I am going to present.

[Slide]

The primary outcome variable in both groups was conversions, that is the need to stop using the method that the patient was randomized to and use a different method to complete the procedure.

I am going to present the conversion results in two ways, one which includes data before the system was even brought to the operating table, and what is involved with that will also be presented by Dr. Gardiner. He will make that clear as to what part of the surgical procedure does take place before the Intuitive System is even in place.

In that case, the protocol did not specify test of equivalence. Only note here that in this case, in this period of the intervention there were two conversions in the lap chole arm and one in the lap Nissen arm, both using the Intuitive procedures, two and one occurrence respectively in these proportions, 3.5 percent and 1.7 percent.

[Slide]

Our intent was to test for equivalence for conversions when the Intuitive instruments were actually used, and that is what I mean by "during the ISI segment." Clearly, you can't have an Intuitive System actually in place in the control group but there is a corresponding

surgical interval and that is what is meant here.

In this particular case there were no conversions either in the control group or in the Intuitive group for either study. The N/A for the p value simply means that one can't calculate a test of substantial equivalent; you can't divide by zero; the standard error is zero.

[Slide]

The other primary outcome for efficacy is only applicable in the lap Nissen study, called the DeMeester score, and this will be described by Dr. Gardiner. The delta, which is in the middle of the table -- now, this is continuous outcome -- is 14.8 divided by 6. Notice at the top the estimated control value was equal to 6; the 14.8 is what DeMeester published as the thresholds. If a person has a DeMeester score over 14.8, that is considered to be abnormal and a score lower than 14.8 is considered to be normal.

Notice that at the bottom of this transparency I have something called the minimum delta. This is the delta so that if you take the evidence from the trial into consideration the p value would be exactly equal to 0.05. That is, if a delta is prespecified and equals 1.71 or larger, then the difference between the observed ratio, which is directly above that bottom line, 1.02, and 1.07, the data would support equivalence at the 0.05 level.

Again, I want to remind you that low p values means that we have established equivalence.

Notice in the middle of the table again that the actual ratio, 2.5, is considerably larger than 1.71 and, of course, that is why the p value is so small. It is less than 0.001.

[Slide]

The primary safety outcome is complications. Again, we have the period prior to the instrumentation being used, even being brought to the table. This was not intended for a test of equivalence and that is why the delta is not specified. But for information, we did observe 2/57 cases in the lap chole group versus 3/60 in the lap Nissen groups in the Intuitive treated arms versus zero in the control arm for the lap chole and 5 percent in the lap Nissen arm.

[Slide]

What was meant is to compare complications as a primary outcome again during the segment in which the Intuitive instrumentation was actually in place. As with conversions, there were no occurrences in either arm for either study.

[Slide]

One of our secondary outcomes is procedure duration. I would like to read this quote that is in the

protocol: "Our clinical consultants maintain that for laparoscopic procedures the operative time would need to double -- that is where I have 89 times 2 or 178 in the previous example -- before we would begin to be clinically significant. For purposes of final analysis, a conservative delta -- and I would like to underline "conservative" -- of 45 for lap chole and 50 for lap Nissen minutes will be used.

[Slide]

You will notice in the middle of this table that there are two deltas. There is a ratio delta, and I said conservative, and a ratio delta equal to acceptable. In the protocol, and this is confusing, we have 1.5 as the ratio delta to be considered for the lap chole arm, but we also have in this quote that we could use the delta equal to 2.

Now I want to draw your attention to the bottom of this transparency where, again, the minimum deltas are listed, 1.76 and 1.71. Again, the idea is very simple. If the delta that we prespecified was greater than 1.76 then the evidence of the data would support equivalence. If we had chosen a value that was lower than that -- and, remember, this is a parameter you choose up front -- then it was too conservative. But we admit that we were choosing a conservative one so I hope you will bear with this in this regard. Notice that the p value is less than 0.001. We established equivalence used in the deltas of 2.

[Slide]

The final outcome that I want to refer to is postoperative stay, again a secondary outcome. The estimated values from the controls in the literature were two days and three days on average for the lap chole and lap Nissen studies. This is a continuous outcome so we are using a ratio delta, and the clinicians deemed that an average of three days for the lap chole group was acceptable, hence the ratio of 1.5 -- 3 divided by 2, and also the ratio of 1.5 for lap Nissen, which means that up to 4.5 days would be clinically acceptable for postop stay for lap Nissen cases, again with a delta of 1.5. In both cases equivalence is established, noting again that the p values were less than 0.05.

[Slide]

I think now I would like to stop this presentation and Dr. Gardiner will present the study findings and speak to the clinical interpretation of the data.

Clinical Study and Results

DR. GARDINER: Good morning. I would like to thank the FDA and all the panel members for the opportunity that they have given us to make this presentation today.

I am a general surgeon, and my focus today is going to be on the clinical importance of the data rather than the statistical one. I am a surgeon in northern

California with an active clinical practice in advanced laparoscopic surgery. I have been a consultant to Intuitive Surgical since April of 1996 and at the outset, and in the interest of full disclosure I should mention that the company does compensate me for my time through a consulting agreement, and I do have a small equity position in the company.

In July of last year the company began a clinical trial, clinical study to demonstrate that the Intuitive System can be used safely and effectively in performing laparoscopic surgery.

[Slide]

I was the principal investigator for that trial and over a three-month period we completed 129 laparoscopic cholecystectomies and laparoscopic fundoplications using this system. We did 12 training cases and 117 randomized cases as part of the clinical trial.

As we begin to examine some of this data today, we are going to see that there are some differences in some of the data and some of the values between the control groups and the study groups. When these differences are put into clinical context, and the appropriate clinical context, I think you will believe and see that none of these differences are actually clinically important, and that the data does adequately support the conclusion that this system

can be used safely and effectively in both basic and advanced laparoscopic procedures.

[Slide]

This was a prospectively randomized clinical trial concurrently run that included 12 training cases and 233 randomized patients that were operated on between July and October of last year. Now, there were two procedures that we evaluated in this trial. One was the cholecystectomy, a procedure that is probably the most commonly done and one of the most basic of laparoscopic procedures. The Nissen fundoplication is a procedure requiring advanced laparoscopic skills and suturing techniques. In each arm of the study, both the cholecystectomy arm and the Nissen arm, the patients were randomized into one of two groups, a control group in which the procedure was done with conventional laparoscopic technique and traditional instruments and a study group in which the procedures were done using the Intuitive surgical device.

In prospective collaboration with the FDA, the company chose to do this trial at Hospital Torre Medica, in Mexico City. This is a three-month trial and the company was unable to locate any center in the United States in the available time that had a sufficient number of patients with sufficiently severe, untreated gastroesophageal reflux disease to meet the inclusion criteria. We had a full-time

clinical monitor present on site throughout the study to ensure accurate and complete data collection and patient follow-up.

[Slide]

Four completely separate surgical teams participated in this study, each with their own assistant and their own scrub nurse. These four surgeons were all very highly experience laparoscopic surgeons. On average, each of them had done over 1000 laparoscopic cholecystectomies and 400 Nissen fundoplications using conventional laparoscopic technique and traditional laparoscopic instruments. I think you will see as we get into the data that this will need to be considered as you interpret some of the data that we present today.

[Slide]

This is a photograph of the operating room at Hospital Torre Medica. The surgeon's console is over on the left. The patient is on the right, undergoing a cholecystectomy. The Intuitive device is in place here and the assistant is positioned between the patient's legs with the scrub nurse to his direct right.

[Slide]

In the cholecystectomy arm of this trial only patients with symptomatic gall stones, documented on ultrasound, were included. Patients were randomized

preoperatively, not intraoperatively. As a result, there were no intraoperative exclusions specified in the protocol. So, in essence, this data is being analyzed on an intent-to-treat basis. Morbidly obese patients were excluded, as were those requiring emergent surgery because of acute cholecystitis. In an attempt to try and reduce variability between treatment groups and control groups, patients with the suspicion of common duct stones that would need a common duct operation in addition to a cholecystectomy were excluded preoperatively. Finally, any patient that had a relative or absolute contraindication to having their disease treated laparoscopically were excluded from the trial preoperatively.

[Slide]

In the fundoplication arm only patients with symptomatic gastroesophageal reflux disease were included. This required that they both had endoscopic-proven, biopsy-proven esophagitis, and that the DeMeester score was over 14.8. For those of you not familiar with this test, it is a measure of the severity of acid reflux from the stomach up into the esophagus.

As in the cholecystectomy arm, in an attempt to try and reduce patient variability between control and study groups, we excluded patients with morbid obesity, patients with intrinsic esophageal disease, and patients with

periesophageal hernias since that is fundamentally a different condition and, in addition, like the laparoscopic chole series, any patient with a relative or absolute contraindication for laparoscopic was excluded. As in the cholecystectomy arm, there were no intraoperative exclusions defined.

[Slide]

Remember, this study was done from a clinical point of view to demonstrate that the Intuitive System is safety and effective in performing laparoscopic surgery. That is what the object was. The endpoint in both the cholecystectomy and fundoplication arms to establish safety was equivalent complications, equivalent complications occurring in the study group compared to those occurring in the control group. I believe you will see that we met this endpoint from a clinical standpoint and, in fact, in many ways patients in the study group fared considerably better than those in the control.

We also had a series of endpoints related to effectiveness. In the cholecystectomy arm the primary goal was to successfully remove the gallbladder without conversion to either conventional laparoscopic technique or open surgery.

There was a series of secondary endpoints -- equivalent procedure time, equivalent postoperative hospital

stay, and comparable quality of life scores. This is a psychological well being test that is a measure of quality of life.

[Slide]

The endpoints for safety and effectiveness for the fundoplication arm were identical to those in the cholecystectomy arm, with one exception. There was an added primary effectiveness endpoint that was the equivalent reduction in the DeMeester scores following surgery between the control and the study groups. Otherwise, the Nissen arm and the cholecystectomy arm were the same.

[Slide]

You are going to see some differences between the control group and the study group in several of these effectiveness endpoints, primarily as it relates to procedure duration. I believe we understand why some of those differences occurred, if not all of them, and we will go into that in a little bit more detail in just a little bit. But you will see that none of these differences are clinically important, and certainly not sufficient to conclude that this device isn't clinically effective.

The evaluation of safety of this surgical device is based on a comparison of complications that occurred between the study group and those that occurred in the control group. It, therefore, becomes very important that

we understand why each and every one of these complications occurred in this clinical trial. To do so, we need to know precisely what part of each procedure the study device was used for.

[Slide]

In each cholecystectomy the abdomen was initially insufflated and the trocars were placed in a traditional and usual fashion. In the control group all the remaining steps of the cholecystectomy were done with conventional laparoscopic instruments, using traditional laparoscopic techniques. In the study group it was only after the trocars were in place that the Intuitive System was introduced into the patient. Once that had been done, the remaining steps of the operation were done with the Intuitive System. This is the reason that trocar injuries have nothing to do with either the use of or the safety of this device because the trocars were placed before the Intuitive System was ever introduced into the patient. After the gallbladder has been dissected from the liver bed the system is removed, the gallbladder is removed with traditional instruments, and the trocars are then removed and the incision is closed in the usual fashion.

[Video]

The study device in this video is being used on the left and standard instruments are being used on the

right. The gallbladder is initially freed from the surrounding structures here. Clips sufficiently large to occlude the cystic duct and the artery that goes to the gallbladder were unavailable in the Intuitive System at the time this study was done.

For this reason, once the duct and artery were completely dissected they were clipped on the patient side, and you may actually see a clip here and over here, using the conventional clip applier in both the study group and the control group, and then both were doubly tied using intracorporeal knotting and suturing techniques. The gallbladder was then separated from the liver bed, after the cystic duct and artery are divided, in the study case being done with blunt dissection and cautery with control. You can see the advantage that the articulated end of this instrument has in terms of directing the tip of the instrument to the tissue. In the study group the Intuitive System is removed after the gallbladder has been extracted using conventional instruments.

[Slide]

In assessing the comparative complications in the fundoplication arm of this study, it is just as important as it was in the cholecystectomy arm that we understand what part of each procedure the device was used for, and you will see why that is important as we get into the data. In each

fundoplication procedure the abdomen, just as in the cholecystectomy, was insufflated in the usual fashion; trocars were placed, as they would be in traditional laparoscopic surgery.

Now, harmonic scalpel was not available on the study device at the time this trial was done and, therefore, in both study groups and control group the short gastric vessels that tether the stomach to the spleen were cauterized, divided and taken down as the next step in the operation. So, we put the trocars in, divide the short gastric vessels with the harmonic scalpel, and this is all done using traditional laparoscopic instruments and is identical in both groups, whether it is the control or the study group.

In the control group the remaining steps of the operation are then completed using traditional instruments and conventional technique. In the study group it was only after the division of the short gastric vessels that the system was introduced into the patient. This is the reason that neither trocar injuries nor harmonic scalpel injuries produced during the operation have anything to do with either the use of or the safety of this device because the device hasn't been brought to the table prior to the trocars and the short gastric vessels being divided with the harmonic scalpel.

Once in place, the system is then used to do the rest of the operation and the fundoplication is completed, anchored to the crura, and then once the operation is finished the system is removed and then the trocars are removed and the incision is closed in the traditional and conventional fashion.

[Video]

A study case is being done on the left, a control case being done on the right. The initial step of the operation in both study group and the control group is to divide the short gastric vessels with the harmonic scalpel, and that is being done here. So, you can see that the system at this point has not been brought into the field. It hasn't even been brought up to the operating table at this point, and the control and the study groups are being done with the same instruments.

Once the Intuitive System is brought into the field, the right crus is dissected and, once the hiatus has been freed up, the fundus is brought underneath the esophagus and that is happening here. This is the esophagus. Then the fundal wrap is sutured together in front of the esophagus here using intracorporeal suturing techniques and intracorporeal knotting. You can see once again the advantage that this articulated instrument gives you here in terms of having the tip of the instrument

directed toward the tissue in the proper orientation. The crura are then closed and the wrap is then anchored to the crura, and then in the study group the Intuitive System is removed and the trocars, and wounds are closed in the traditional fashion.

[Slide]

There was a total of 245 patients enrolled in this trial, 129 patients in the study group and 116 controls. Of the patients that were enrolled on the Intuitive side, there were 12 training cases done with the Intuitive System, leaving a total of 233 patients that were actually randomized, essentially equally distributed between the control and the study groups.

[Slide]

There were no meaningful differences between the study group and the control group with regard to age, body mass index or PGWB scores, and on the fundoplication arm, which is the only arm that has relevance to the DeMeester score, the preoperative DeMeester scores were essentially identical.

[Slide]

We completed 245 procedures in three months, roughly divided equally between the two arms of the study and between the control and study groups within each arm. There is some distribution and variation between the number

of cases surgeons did and the distribution of those cases, but those differences were based on patient availability at the time the surgeon was present and these differences are, as you can see, relatively minor.

There were only 12 training cases, 5 on the Nissen side and 7 on the cholecystectomy side, that were done by these 4 surgeons prior to randomization of the patients into the trial. This meant that at the outset of the study none of us had any appreciable clinical experience with this device. The average number of study cases that each surgeon did during the trial was about 29 so that even by the end of the trial our experience was still quite limited with this device, and this may well have contributed significantly to the procedure duration, as you will see later on.

[Slide]

Let's take a look at the results from this trial. Remember that safety was defined in both arms of this study as equivalent complications between the control group and the study group. I will only talk about complications that we observed in this study.

[Slide]

This is an overview of every adverse event that was experienced in these 245-patient study, ranked in decreasing order of severity from top to bottom. The patient who sustained the gastric perforation had by far and

away the most serious complication in this series, and this complication ultimately resulted in her death. This was a patient in the control group, and the complication was due to an unrecognized injury to the stomach, felt to be related to the use of the harmonic scalpel. This was recognized 24 hours following surgery. Multiple reoperations were required for abscess drainage, and this patient ultimately developed adult respiratory distress syndrome and died on the 83rd postoperative day. That is the patient in the control group, the most serious complication.

There were two treatment failures, also both in the control group. Both were due to migration of the wrap around the esophagus, having the wrap migrate up into the mediastinum. The first of these, this perioperative wrap migration, occurred 8 hours following surgery. It was recognized and the patient was immediately taken back to the operating room and re-laparoscoped. The wrap was taken down but the fundus was found at the time of the second operation to have already developed an area of necrosis. This was resected laparoscopically, and the patient was discharged on the 21st postoperative day and has done well. So, that is the first treatment failure, the perioperative wrap migration.

The second treatment failure, also in the control group, was a late wrap migration. This patient is an opera

singer and the patient's reflux symptoms recurred about two months following the original operation. The evaluation revealed that the wrap had migrated into the chest, and this patient required reoperation three months later. This patient is now reported to be asymptomatic and doing well. This wrap migration problem is something that we are becoming increasingly aware of as a recognized complication of the Nissen procedure.

There were two trocar injuries to the bowel in this study, one in a training case and one in a randomized patient in the trial. Neither one was related to the study device since the trocars were put into these patients before the system was even brought up to the operating room table, and that is why I spent so much time emphasizing what part of this operation was done by the study device.

The injury to the small bowel was recognized 24 hours after the original procedure and, again, this is a training case. This patient required reoperation and repair of the enterotomy but she had an uneventful postoperative recovery and was discharged on the 8th postoperative day, and she is doing well.

The injury to the stomach -- this one -- occurred in one of the randomized patients, randomized to the study group. This was recognized intraoperatively, repaired laparoscopically, and the patient experienced no untoward

event.

There was one patient in the study group that developed bleeding from the trocar site, is this one, and was returned to the operating room. This was actually my patient. The wound was re-explored locally and a vessel in the abdominal wall was suture ligated. On review of the tape following this operation, it was clear that the bleeding was related to the initial insertion of the trocar site through the abdominal wall and not related to the study device itself. This patient also had an uneventful postoperative recovery.

There were three minor complications that occurred on the study side of this trial. There were two minor serosal tears to the stomach related to use of the harmonic scalpel. These were reinforced laparoscopically with sutures and were of no consequence. Once again, these occurred before the system was brought up to the patient.

There was a superficial umbilical wound infection. That was also my patient. The gallbladder ruptured in this patient as we were bringing it up through the umbilical incision and stones and some bile were spilled in the incision and I think, most likely, that is what led to this infection. It was a trivial infection and was managed with just warm compresses.

[Slide]

In summary, there were nine complications in these 245 patients. By far and away, the three most serious ones occurred in the control group, including one death and two treatment failures on the fundoplication arm of this trial. There were five complications that occurred in the study group, and none was related to use of the study device. Four occurred before the system had been brought up to the table, and two of these were related to trocar placement and two were related to use of the harmonic scalpel, and there was one minor wound infection with a known antecedent cause. There was one trocar injury to the small bowel that occurred in a training case prior, again, to introduction of the system into the patient.

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Concluding this, from a clinical standpoint, it doesn't appear that there were any device-related complications associated with the use of this system. All of the complications were related to the use of conventional laparoscopic instruments and, in fact, the control group actually fared appreciably worse in this regard than did the study group. The data establishes that the safety endpoints for this device have been met.

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Well, we have addressed the issues of safety of this device, now let's deal with its effectiveness. We have

defined the primary effectiveness of this device by its ability to successfully remove the gallbladder and complete the fundoplication without conversion to either conventional laparoscopic or open surgical technique. Then as a secondary endpoint there was another endpoint for equivalency which was a reduction in the DeMeester score on the Nissen side.

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Let's look and see how we did with regard to these effectiveness endpoints. There were 12 training cases done with the study device; 117 patients were randomized into two groups to have their operations performed with the Intuitive System. All 12 training cases and 114 of the 117 randomized patients had their operation successfully completed using the Intuitive device.

There were three remaining cases that had been randomized into the two study groups but whose procedures were not completed according to this random assignment. These three cases were converted either to an open laparotomy or conventional laparoscopic before the system was ever brought to the operating table. So, there were no conversions after the system had actually been placed into use.

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So we can truly understand what happened in these

patients, because I think it does go to the issue of effectiveness and these primary effectiveness criteria, let's go into a little more detail about what happened in these three cases. There were three patients that had been randomized into the study arm but in whom the Intuitive System actually was never even brought to the operating room table.

The first case was actually my patient. We inserted the laparoscope and immediately found severe macronodular cirrhosis, and this patient had extensive portal hypertension. I just felt there was an absolute contraindication to proceeding with any form of laparoscopy and I basically removed the laparoscope and immediately converted this patient to an open laparotomy and completed the patient in the traditional open fashion.

There were no intraoperative exclusions defined in the protocol so technically, for the purposes of this analysis, this patient has been considered a conversion. The study device, however, was never actually inserted into this patient, and had the pathology of this patient been detected preoperatively he wouldn't have been allowed to participate in the clinical trial in the first place.

The other two cases that were not completed according to random assignment were completed using conventional laparoscopy. Let's talk about those two. One

of these patients had severe acute cholecystitis, severe acute inflammation and scarring in the porta hepatis, and the other had a very significant nodular cirrhosis. These two cases were Dr. White's, and at this point in the trial he had done one training case with the system. These had been his first and his third randomized patients in this trial using this device. Given the severity of the pathology he was dealing with, and his inexperience with the system, he made a clinical judgment that it was in the best interest of his two patients that he use instruments and techniques with which he was already very familiar.

He converted both of these cases without ever bringing the system to the patient's table because of his position on the learning curve and the severity of this pathology. Dr. White is here today with us, if any of you have additional questions about either of these two cases.

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With these three cases in mind, let's review what the protocol actually says about conversions. The endpoint for primary effectiveness of this device was defined in the protocol as successful completion of surgery without conversion to either conventional laparoscopy or open technique. That is what the protocol says.

Now, this definition was well intentioned, but in retrospect it fails to take into account that conversions

can occur and may occur for reasons other than those related to the device itself, and that is exactly what happened in these three cases, and it wasn't anticipated. This has led to a curious situation of having us rely on cases, in which the system was never actually used, to draw conclusions about how well the device works.

Since what we are trying to do here is to evaluate how effectively a surgical device can be used in surgery, it would seem that a better definition for conversion would be terminating the use of the device once the surgeon has started operating with it. Interpretation of the protocol in this fashion would lead to a more meaningful evaluation of the effectiveness of this device since it would rely on cases in which the device was actually used instead of those in which it was never used.

If the protocol is interpreted in this fashion there were no treatment-related conversions in this trial. This seems, to me, to be a more clinically appropriate definition and, given this interpretation, this device clearly met its primary effectiveness endpoint with respect to conversion.

On the fundoplication arm of the study there was an additional primary endpoint for effectiveness, and that was equivalent reduction of DeMeester scores following surgery in the control and the treatment groups.

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There was no difference between the study group and the control group in either the percent reduction of the DeMeester score following surgery, 65 percent and 69 percent respectively, or in the number of patients whose postoperative DeMeester score returned to normal, in this case 39 patients in both study and control groups.

[Slide]

This slide shows you a graphic representation of the DeMeester score data from the preoperative data to the postoperative data, with the control group on the left side, the study group in the middle and DeMeester's classic data that was published in June of 1995 on the right. It is clear that there is no real substantial difference in any of these three groups.

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So, I think the data does show that this device is effectiveness in carrying out basic and advanced laparoscopic surgery. Every procedure that was begun with the device was successfully completed with the device. In the fundoplication arm of the study the reduction of DeMeester scores was equivalent. There were no conversions that occurred that in any way we could attribute to a system failure, that the system wouldn't do or couldn't do what it needed to do or what it was designed to do, or that the

surgeon started with the system and couldn't get the operation finished with the system. Those were the issues that we felt we were addressing in conversions.

So, in my opinion, from a clinical point of view, had any of those issues occurred it would have gone straight to the question of efficacy of this device, but none of those issues did occur. What did happen were conversions related to discovering a contraindication to laparoscopy or the insecurity of a surgeon being randomized to operate with a brand-new device in a very difficult situation. The data shows the device has met its primary effectiveness endpoint.

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There were three secondary effectiveness endpoints that were defined in the protocol, procedure duration, postoperative hospital stay and quality of life scores. In looking at the procedure duration, on average it took us about 40 minutes longer to do the cholecystectomies in the study group with the study device than with control instruments, and it took about 50 minutes longer to do the Nissens with the study device compared to standard traditional laparoscopy.

Now, I don't believe those differences are sufficient to have a negative clinical impact on patient care or treatment outcomes. They are just not sufficient to be clinically important. But as a surgeon, and having spent

a significant amount of time operating on this system, I have to ask what in the world was it that caused this difference. Why did it take us longer to complete the same procedures using the Intuitive System compared to the control traditional laparoscopic instruments? It is actually a very interesting question.

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I have looked at a great number of the tapes of all four of us operating, and in my opinion there are a number of factors that have contributed to these longer procedure times. Probably the most significant factor was that this was a completely new device being used clinically for the first time by all four of these surgeons. As you watch these tapes, it is pretty clear that all four of us were gaining confidence in the use of the system as the study progressed. We were obviously more comfortable, all four of us, by the end of the study than we were at the beginning, but it is also obvious that all four of us were still learning how to use this device. Historically, operating times for every laparoscopic procedure, including the lap chole, have fallen as experience has been gained, and it will be no different for this device.

Secondly, it is clear when you actually watch these videos, and I have watched a lot of them, that the movements made by the surgeons with the device are

definitely more deliberate; they appear to be more meticulous, more precise, but they take longer to make.

The third factor I believe is that having the surgeon sit next to the patient at a console changes the dynamic between the surgeon and the assistant. Surgeons using this system need not only to learn how to use the system but they will also need to learn how to use their assistant in a more effective and the most efficient manner. This is going to take some time and some experience, I think, with the system to do that, and I think it is going to be a unique and different process for each individual surgeon as they work through the experience curve.

Finally, time is required to set up the device, 7 minutes for the cholecystectomy and an average of 14 minutes for the fundoplication, and this needs to be added to the procedure duration.

So, as you might expect, procedure duration was, in fact, affected by the use of this device and it is a multifactorial issue. But in the final analysis, even if the procedure duration stays the same, which it almost surely will not, it just isn't sufficient to be clinically important.

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Now let's look at length of stay. According to the protocol this outcome has been analyzed on the basis of

mean length of stay. On this basis there is no significant difference between the control group and the study group in the cholecystectomy arm of this study, being 1.3 days for each group. In the fundoplication arm, this arm here, the length of stay is artificially high in the control group, 1.4 days for the study group and 3 days for the control group. This longer length of stay is because there were 2 patients in the control group who suffered major postoperative complications, and when you take these 2 cases into account and you analyze the data that way there just aren't any clinically important differences between control and study group in either arm of this study with regard to length of stay.

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The improvement in quality of life scores basically show no significant differences between study and control groups but there were some additional observations that were noted during this study that, although they were not defined in the protocol as either safety or effectiveness endpoints, deserve some comment.

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Dysphagia is a common and well-recognized complaint in the early postoperative period in patients undergoing fundoplication. There were eight patients in this trial that underwent dilatation following surgery,

three in the control group and five in the study group, and all of those patients are now asymptomatic. These differences are not statistical significant.

Blood loss in this trial was trivial in both control and study groups and in both arms of the study. That having been said, there was an observed difference in the average blood loss between control and study group in both arms of the study. There was a difference of about 13 cc in the cholecystectomy arm and not quite 12 in the fundoplication arm. Now, this amount of blood, just to put it into perspective, is a little over 2 teaspoons, and it is actually less blood than the amount of blood that was drawn from these patients to do their preoperative lab testing. This amount of blood loss is just clinically unimportant.

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The system performed, with regard to reliability, very well and it performed as it had been designed throughout the course of this clinical trial. The system-up time was 99.7 percent. There were 3 system faults that occurred in 3 separate cases for a total down-time of 13, 20 and 12 minutes respectively. The system behaved as it had been designed to and went into an immediate "safe" state. The device was successfully rebooted in all instances and the procedures were completed without further incident. There were no adverse event outcomes as a result of these 3

faults and the software has been modified to eliminate them.

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In conclusion, there were no device-related complications that occurred in this study. So, the safety endpoint has been met. All of the procedures that were begun with the Intuitive System were successfully complete with the Intuitive System, and the reduction in the DeMeester scores in the study group was equivalent to that in the control. So, the primary effectiveness endpoints have been met. Based on the clinical data, there is a reasonable assurance that the Intuitive System is both safe and effectiveness when used in accordance with its intended use.

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Now, from a regulatory point of view, this device has already been cleared through the 510(k) pathway for blunt dissection, retraction, stabilization and manipulation and control of endoscopes. With this limited array of tools, the system is basically an assisting device.

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What the company is seeking is to have this additional indication for use added to the labeling for this device that would allow tissue grasping, sharp dissection, suturing and use of the electrocautery.

[Video]

This additional indication and the tools it covers will enable surgeons to actually use this system clinically to safely and effectively perform laparoscopic surgery.

Thank you very much.

DR. WHALEN: Thank you, Dr. Gardiner. I would ask that each of the sponsor's presenters be near or at the main podium to answer any questions the panel may have, and while we may be asking those questions I would like to ask the others of the sponsor's group at the table if they would be kind enough and begin clearing from there in anticipation of FDA assuming that position very shortly.

Are there any of the panel members who wish to ask any questions or make any specific comments to the sponsor at this juncture? Dr. Galandiuk?

DR. GALANDIUK: I have two questions. Looking through the materials that were sent to us ahead of time, it listed in the device descriptions that it was for use by a "professional" and I was just concerned that this might be of use by nurses, and I think it should be intended for use by surgeons and I think that should be stated in the label.

The second question is for Dr. Gardiner. Considering that he, as an expert who used this device, took longer to do his operations with this, whether is the extent of the learning curve? And, if this new indication is approved, how will that be addressed by the company in terms

of teaching surgeons how to use this or giving them, you know, the 12 training cases that the investigators had here or some significant experience so that they know how to use this?

DR. GARDINER: I think the learning curve is always a difficult issue. Having been involved in the development of choloresection, for example, laparoscopically, it took me 65 or 70 cases before I was really comfortable that I could do those operations with equal facility to open surgery. Now, I don't think it is going to take anywhere near that degree of training on this device. It is pretty clear to me that you are safe and effectiveness sitting down and operating with it initially, but there is no question you are going to get better as you go -- I don't know, 10 or 15 cases maybe. But I think that the learning curve is going to continue much beyond that. In terms of training, what the company is going to do about that I don't know. We probably ought to have Dr. Moll handle that.

DR. MOLL: Just to remind you, there were 12 training cases in this study distributed between 4 doctors. I think in one sense surgeons never have enough training but, clearly, training is a very important part of this story and will be a very important part of how this system is introduced. There is no surgical device that is

introduced and is immediately picked up by the surgeon and used properly without training.

I won't go into specific plans about how the system, if sold in the United States, will be trained. I am probably not the right person to do that, but it is at the top of our mind and we will have very clear plans for introducing a training protocol together with the sale of this device.

DR. GALANDIUK: How is the training conducted in Europe?

DR MOLL: In Europe it begins with bench-top training. In other words, you remember from the video that the system is used in the lab and the surgeons and the surgical assistants are brought in and have a very thorough, didactic overview of the system, its capabilities and sort of a general philosophy of how it works and how the system architecture is designed. Next, the surgeon and the surgical team have an opportunity to spend a lot of time on the bench-top suturing and performing dexterous tasks, and just using the system, moving their arms around and understanding how it is placed in the operating field, how it is draped, and all the things that go along with proper setup. Once the proper didactic and bench training is performed, we then sponsor a number of cadaver labs and animal labs where the system is used both in animal tissue

and in cadaver tissue to understand, again, proper setup and the limitations of the system, and how it is ideally set up and how it works most effectively.

So, it is bench-top training, didactic training, animal training, cadaver training extensively before it is introduced clinically. Obviously, it doesn't stop there. When we introduce it clinically we have both a proctor that is required to be on site to walk the new investigators and the new users of the system through the first cases. We also script very carefully what they do and what they do not do with the system, such that people walk before they run with the system. Most of the time they begin with open procedures. In other words, they use the system in an open case before they are asked to do minimally invasive technique. So, it is an extensive process of making sure that before there are procedures that challenge the surgeon's familiarity with the device he has an extensive period of getting comfortable and he understands the basics of the system.

Having said that, as Dr. Gardiner mentioned, surgery is all about experience, and there obviously is going to be a learning curve with this system as with any other surgical device. But we take very seriously the need for training as a part of the story.

DR. ANDERSON: I have just a few questions. Dr.

Moll, in terms of the prior experience with these tools in practice -- I can see that because of the articulation the system has a lot more nooks and crannies than your standard laparoscopic tools. Are there any problems with cleaning these devices in comparison to those other tools, and things getting caught inside those delicate articulations?

DR. MOLL: Yes, they are based on a cable and pulley system so there are areas of the wrist where that mechanism is exposed. Having said that, they have been designed to be cleaned and sterilized such that they have flush ports where fluid can be run through the inner parts of the system so they can be thoroughly cleaned and sterilized. Our experience in now 400 or more cases is that we have not seen any problem with cleaning or sterilization of these instruments.

DR. ANDERSON: Does that mean that there do need to be special instructions about how to clean these devices in comparison to other devices?

DR. MOLL: I think absolutely there need to be special instructions in the labeling as to how the instruments are best cleaned and sterilized.

DR. ANDERSON: I also have a question for Dr. Gardiner, if I could. I just want to make a comment. You talked about the protocol and when you randomize. I think you reported your data correctly by doing it from the time

of randomization because otherwise patient selection gets introduced that screws up the randomization principle. But I do have a question from a technical, practical standpoint. The two procedures that you are talking about are not procedures commonly associated with major bleeding but we can imagine that with time surgeons are going to try different techniques, and thinking of a laparoscopic splenectomy maybe you could get into a major vessel injury during this and you, as a surgeon, are sitting across the room from this. You are not scrubbed in at that point. Your hands are on the controls. What if you got into major bleeding and you needed to get into that abdomen quickly? How can you imagine that happening in a way that is safe and not life-threatening for the patient?

DR. GARDINER: Well, we are really not sitting across the room, we really are, certainly in vision, sitting next to the patient; not in the sterile field but next to the patient. You know, bleeding is a problem with any laparoscopic procedure and, certainly, that was a lot of our concern when we first started doing laparoscopies -- what happens if you have to convert? Well, you make an incision and convert. As I think you can see from the video, it takes just a second or two to get that system out of the way if you need to convert, and it is a matter of gowning and just stepping up to the table.

DR. ANDERSON: But the difference is you are not scrubbed in; you are not sterile, unlike a standard laparoscopic procedure. So how would that happen? Do you need to have somebody else standing by? Your assistant?

DR. GARDINER: The assistant is standing by. This is not intended to be used, you know, as a stand-alone instrument. So, you do have an assistant at the table.

DR. CRITTENDEN: The assistant needs to be a surgeon?

DR. GARDINER: I think that is a good question.

DR. CRITTENDEN: Given the scenario you are talking about, it sounds like it.

DR. GARDINER: Yes, you know, certainly whether the assistant is a surgeon or a PA, that certainly varies from community to community. Certainly, at this point in time we would envision that a surgeon would be an assistant.

DR. TALAMINI: In this case, wasn't the surgeon at the console scrubbed, with gloves and already sterile, or did I misread that in the protocol?

DR. GARDINER: That is true.

DR. TALAMINI: So, the surgeon would just need to take the gloves off or gown off and they would be sterile already, or not?

DR. GARDINER: Right. No, that is correct. You probably would want to strip the gown off or put a new gown

on.

DR. TALAMINI: I have two questions, and as a clinical investigator these are a little hard for me to ask but I think I need to ask them. First of all, perhaps for Dr. White or Dr. Gardiner, the two cases that you described in detail where it was elected, once the laparoscope was placed, to not use the system, the fact that those two cases were withdrawn early in the study, did that skew the results? In other words, were there equally tough cases later on that were completed using the device? That is one question.

The second question is it seems to me, with a general knowledge of the literature, that the gallbladder rupture rates and two trocar injuries in 200 patients are on the high side for those incidents. I guess I feel like I need you to help me with why that doesn't contaminate the rest of the study. I understand that many of those things occurred when the system was not in place, yet they are there and they are part of the results, and I need you to help me with why that shouldn't contaminate our interpretation of the remainder of the results when the system was in place.

DR. GARDINER: Well, none of those complications occurred while the system was in place. So, these are complications that occurred during the traditional standard

conventional laparoscopic part of the operation. So, it has really nothing to do with the system. Why they happened? I don't know. I mean, I can tell you that these surgeons were very experienced. Actually, two of the injuries occurred to Dr. Cadiere. I have watched him operate. He has an extraordinarily fine reputation, and I don't know why they happened to him in this study. I can't answer that. But I don't think that they had any relationship at all to the use of the system so it is really two kind of separate questions, it seems to me.

With regard to all of these complications, I think it goes to the serosal injuries to the stomach, as well as gallbladder perforation. We have been very rigorous in what we looked at and if there was a drop of bile that leaked out during the case, it was counted as a rupture. So, I think that we have perhaps, if anything, skewed the data to a more critical side and I think that is probably the explanation for the gallbladder issue. But these injuries that occurred in the traditional part of the operation -- I struggled with why they happened and I don't know.

I mean, I can tell you that with that case that I had with the abdominal wall port site bleeding -- I can't remember when that has happened to me but, here we are, dealing with it. So, I don't know.

DR. FERGUSON: Could I ask a question of Dr.

Gardiner? It gets back to the gowning and gloving aspect. The four surgeons who did these cases, did they gown and glove as we read in the protocol, or did they not do that?

DR. GARDINER: No, they are gowned and gloved but, you know, you are not sterile obviously --

DR. FERGUSON: Not scrubbed?

DR. GARDINER: Right.

DR. FERGUSON: So, it is not a matter of putting on a gown and gloves, like you might do in some cases, scrubbing first and then gowning and gloving and being able to change quickly if you needed to.

DR. GARDINER: That is correct. I mean, you could certainly do that.

DR. FERGUSON: The reason I am pursuing this is that I think the issue is important as the device is disseminated because this is a true difference from a surgical situation, and I think it needs to be emphasized.

DR. GARDINER: We would certainly agree with that. We did not address the issue of those two cases of Dr. White's.

DR. WHITE: Mr. Chairman, panel members, Alan White, Tacoma, Washington. I am a general surgeon by training. I practice in a multi-surgical group, six of us, and our chief emphasis is in laparoscopic breast and colorectal surgery. In addition, I am the medical director

of the Multi-Care Health System Endosurgical Institute, in Tacoma, Washington, where we give advanced laparoscopic training and proctoring and precepting to surgeons in private practice.

Specifically, would you repeat the question in regard to the two patients that were converted in my series?

DR. TALAMINI: My only concern, sir, was whether the removal of those two cases early in the study had the potential to skew the data. The other side of the coin would be were there equally difficult cases later on in the study that were accomplished with this device that would eliminate that possibility of the data being skewed by early removal of those cases?

DR. WHITE: First off, I am not a statistician so I can't address the skewing of the data. I would defer that to our statistician. Specifically though, in the conduct of the procedure and what we saw and did as this, my first and third randomized events, let me take you there.

Specifically, I had done the day before a training procedure using the ISI system for laparoscopic cholecystectomy and a laparoscopic Nissen. Both were standard cases with no obvious or significant and severe pathology. On my very first case on the first randomized day, my second day in Mexico City, I put the scope into the first case and encountered a cholecystitis that, having done

probably 2000 laparoscopic cholecystectomies, I would count in the top five as far as severity, a case that had both severe acute and chronic inflammation.

At that time, I held the procedure in abeyance. I called the on-site coordinator and we discussed it at that time and, based on my understanding of the protocol at that time, I was under the impression that we could make an intraoperative exclusion. That is, we found something that should have been found ahead of time and we were not aware of. Discussing it at that time, I opted to say clinically this is a case that I don't believe I can do laparoscopically. Therefore, my option is made to convert.

Conversion is a term that we have had to struggle with in laparoscopy since its inception, that is, conversion to an open event is not bad. At that point in time, with my level of training with the system being rudimentary or at least not sophisticated, I opted not to use the system on that case but, rather, proceed to an open event, and I opted to use standard laparoscopic technique, and went ahead and proceeded with the case in that way.

The third case was much akin to the one Dr. Gardiner reported. Again, that same day, a case where, on placement of the scope, both macronodular cirrhosis and portal hypertension were found and, again, with that same reasoning the same series of events occurred.

Later in the trial I probably did cholecystectomies and Nissen fundoplications as severe as anything that was seen, obviously, on that day. But on that day, clinically I was not willing to proceed with the device.

DR. TALAMINI: Thanks. Obviously, that was the wise thing to do.

DR. WHITE: I don't know about wise but it was what happened and it is reported.

MS. DUBLER: I have two questions and I think they are probably for Dr. Moll. The first has to do with the structure of the study itself. You said that in the three months of the study there was no site outside of the one you chose that had sufficient numbers of cases. Was that correct?

DR. MOLL: That is correct.

MS. DUBLER: Why did you limit it to three months? What was so important about that that you could not collect other sites and see if there were any possible differences among the sites in how the study proceeded?

DR. MOLL: There were financial considerations and there were considerations about the availability of the system. We had one system that was available and able to be used for this trial. So, rather than accomplish a multicenter study, we believed that in the interest of

efficiency we could have surgeons come to one site and use the system rather than -- which would have been impossible at the time -- move the system from site to site, because we only had one system. So that was sort of the overriding feature.

I don't have the data but we very carefully looked at the number of procedures performed in this country, laparoscopic Nissen fundoplications, and although I am not sure of the total number it is spread out among a number of centers, and to accomplish this number of procedures under one roof anywhere else seemed virtually impossible in a reasonable period of time that we could financially afford to do. I think that was the major point.

MS. DUBLER: I have a second question, and that has to do with the informed consent process that you used and the result of that or the reflection of that in the informed consent form that was presented to your patients. In the form that I reviewed just today there are no benefits suggested for this procedure.

DR. MOLL: Correct.

MS. DUBLER: And there has been a discussion today of equivalence but not of benefit and, therefore, my question to you is what is the benefit of this procedure?

DR. MOLL: Yes, I tried to address a little bit of that up front, but it is a very good question and a question

that clearly comes out of the study the way it was designed. This was an equivalence study. We had no intention of trying to prove that this surgery was somehow better than conventional technique. So, I think it gets back to the capabilities of this system in surgery, in minimally invasive surgery, that although the benefits in a routine gallbladder surgery may be very hard to describe and, in fact, there probably aren't any, I think you would agree that if a system is safe and efficacious from the standpoint of being able to do the procedure and deliver more dexterity intraoperatively than the surgeon is accustomed to with conventional technique, then we believe that efficacy and the benefit will come from this technique.

Now, there is anecdotal evidence that has to remain anecdotal at this time about what the system can offer. I think Dr. White can describe for you a situation in one of his cases where he needed, because of the dilation of the cystic duct, to suture ligate the duct. I don't want to speak for him but I think is very difficult, if not impossible to do with conventional laparoscopic technique. It is those sorts of situations where articulation and control can really add true benefit to a routine laparoscopic procedure, and I think as procedures get more complex the benefits of the system become more apparent.

MS. DUBLER: Let me just have one brief follow-up

question. Was this protocol reviewed by an IRB in the States, even though it was instituted in Mexico?

MR. DANIEL: Yes, a very similar -- I can't say identical; I would have to look it up, but a very similar protocol was, in fact, reviewed by Summit Medical's IRB.

MS. DUBLER: By whose IRB?

MR. DANIEL: Summit Medical, the hospital in Oakland, California where Dr. Gardiner operates. We had anticipated a possibility of proceeding at that location early on, before we got up to the numbers that we ended up getting. My memory is that there is virtually no difference there but, of course, we did have an ethics committee in Mexico.

MS. DUBLER: I just want to point out what is puzzling to me, given the discussion this morning, given the learning curve, given the teaching cases, etc., that there is no mention in that discussion of the fact that this is a procedure that surgeons are learning to use, which brings with it its own level of risk; nor are there any potential benefits suggested, which puts an IRB in a peculiar situation of weighing articulated risks against no possible benefit that is articulated, in which case it is questionable whether they should permit it to go forward. So, I think that some attention, if this is approved, toward an informed consent process that reflects experience and

possible risk and benefit in a more comprehensive way would probably be advisable.

MR. DANIEL: You may help me because you have it in front of you and I do not, but I remember wording that indicated clearly that the patient's surgeon had a great deal more experience with the conventional tools than he or she would have with the Intuitive System. So, we tried to impart the idea that the surgeon did not have anywhere near close to the experience with the Intuitive System as we the conventional.

MS. DUBLER: Just one very brief question on the experience and how people will be trained. It would seem to me that that experience would need to be quantified in some way, and I wondered whether you have considered a certification process for the use of this system.

DR. MOLL: Yes, we have not closed on exactly what sort of formal training will be required for the system, and I think that is something that deserves a lot of discussion but it is not something that we have addressed to date.

I want to go back and just make sure that there is no misunderstanding on the sterile field issue. The surgeons that performed this trial and the surgeons in our experience in Europe is that the surgeon is gowned and gloved as he sits at the console. So, if there is a need -- and in my recollection I don't remember this occurring in

either the clinical study or the European cases, but if there is a need to step to the sterile field, the surgeon is scrubbed and he needs to merely don gloves and a gown to step to the operative field. So, that does take some time but it can be very rapid if, in fact, there is a need to do that.

DR. CHANG: Just to clarify that, it was my impression, and I would like Dr. Gardiner or Dr. White to clarify that but it was my impression that the clinicians were scrubbed but I would like Dr. Gardiner or Dr. White to say, yes, they were scrubbed during this clinical trial, or perhaps this should be a strong recommendation as a safety feature that a surgeon be available should intra-abdominal bleeding occur.

DR. GARDINER: I think I would agree with you. No, we were scrubbed because the surgeons put the trocars in. So, what would happen is we would scrub and gown just as we would in any traditional laparoscopic procedure, step to the table, place the trocars, then step away and put gloves on so that we didn't contaminate the instrument, and then do the procedure.

DR. MOLL: Just as a sort of backup to that, this was obviously an issue that we struggled with in the design phase of this system and it obviously would be possible to drape and design a console so that it is sterile so that a

surgeon can sit down and remain in a sterile field. We chose not to do that for some very good reasons, that if the surgeon is away from the sterile field it greatly increases the chances of contamination. So, once the surgeon, in the system that we have currently, sits down it is clear that he is not sterile and if he chooses to go back to the operative field he needs to become sterile. So, that was a very clear decision on our part and I think it is the right decision.

DR. CHANG: Dr. Moll, my actual question is that in the protocol conventional clip was used for the cystic artery and duct. So, we truly don't have a sense of the effectiveness if the ligatures by using the Intuitive System. So, in fact, it is belt and suspenders. Are there plans for adding the clip as an instrument? Would this be an addendum to your PMA, or would surgeons rely on the traditional laparoscopic instruments to add that clip in addition to the suture ligature?

DR. MOLL: We will at some point add the capability to deliver large clips to the system. We actually have a system that now can deliver small clips but not large clips. It was sort of a story as to two competing philosophies on what is the best method of ligation of the cystic duct and artery that led to this protocol and, arguably, you know, if we had to do it again we might have done it differently to be more clear about what was doing

the occluding, but maybe I can ask Barry to comment on that.

DR. GARDINER: You are absolutely correct about not making any conclusion about the integrity of the occlusion of the cystic duct or artery because that was done by a clip. In the investigators meeting in sorting this out, three of them used traditional clips and that is the way they did this operation. I happened to tie, that is the way I did the operation and I was agitating for the ligatures and the rest of the investigators felt we ought to do this the way we do traditional surgery, with clips, and that is the way the lap chole is done and that is the way it ought to be done. So, that is the process that we went through to get there. As Dr. Moll said, I think in retrospect we probably would have preferred to do it with just ligatures.

With regard to the integrity of the suturing, of the knot tying, we do have documentation of that with the DeMeester score. If you look at the DeMeester data in the control and the study group, there is no difference between the DeMeester score reduction, and if the knots that this system tied still weren't intact those DeMeester scores would have been different. So, I think we have established the suturing capability by the DeMeester score. That was the reason we chose that particular endpoint.

DR. WHALEN: I am going to ask that other

questions be held in abeyance because we need to get the lunch time. We will have more time for those questions. We will reconvene in this room at 1:30 for a closed session, at which time Intuitive Surgical will have the opportunity to present or discuss any trade secret data that they may or may not have. At two o'clock the public session will reopen and at that time FDA presenters will bring to the microphone the information that we need.

[Whereupon, at 12:35 p.m., the proceedings were recessed, to be resumed in closed session at 1:30 p.m., followed by an open session at 2:00 p.m.]

AFTERNOON SESSION

FDA Presentations

MR. YEN: Good afternoon, Dr. Whalen and members of the panel. FDA will now present a summary of the reviews of this submission.

[Slide]

For your convenience, a copy of all of the presenters' slides are at your disposal. I am the lead reviewer, Dwight Yen, and will give a brief summary of the regulatory and engineering review. Dr. Horbowyj will present the clinical review and Dr. Bushar will present the statistical analysis.

[Slide]

As the sponsor has indicated, the initial system, the initial control system was cleared in July of 1997 for a limited set of instruments, including blunt dissectors and retractors, based on substantial equivalence to other instruments and laparoscope holders already on the market.

At the beginning of this year Intuitive Surgical submitted a new 510(k) for the same control system but adding new instruments, including forceps, scissors, scalpels, clip appliers, needle holders and electrocautery, so that the system can also be used to perform grasping, cutting, electrocautery and suturing.

FDA found the system is no longer substantial

equivalent, or NSE, to an instrument holder because the change in intended use afforded with the new instruments raised different types of questions of safety and effectiveness. Therefore, this device is classified by statute into Class III and is considered a PMA.

The sponsor has already presented a description of their device and principles of operation. FDA considers the device description information factual and adequate. Therefore, very briefly, the system consists of three components -- the surgeon's console, the patient table side surgical cart and the system electronics.

[Slide]

I have reviewed the hardware design, and to the credit of the designer, they have made safety one of the highest priorities, starting with the design, and have implemented numerous safety-related functions in the hardware.

Our software group at the Office of Science Technology provided consultation and review of the software and has determined that the software design and development meets FDA guidelines for software in medical devices.

I will elaborate on the next slide more on this performance testing. Like other surgical tools, material use and the manufacturing of the instruments are considered limited duration patient contact materials. The sponsor has

met FDA guidelines for biocompatibility of each patient contact material that was used.

The instruments are single use and reusable devices that are required to be sterile. Information for sterilization and instruction to clean and resterilize the instruments is adequate and has been validated.

Finally, the system meets the FDA guidelines for electrical medical safety standards and electromagnetic compatibility standards.

In the area of performance testing, two hysteresis studies were performed to evaluate each degree of freedom of the control arm for reproducibility and precision. Six animal studies were conducted to evaluate system setup, port placement, vision and system performance. Four cadaver studies were conducted to evaluate port placement, access issues, tissue manipulation and suturing. Surgeons were invited to use the system to perform a variety of surgical procedures using a porcine heart. Feedback was received in terms of the hand grip design and vision to the system.

A prototype system was used in Belgium, in 1997, for clinical a feasibility study on five patients to initially test the system and, of course, the clinical trial was conducted in Mexico City last year.

[Slide]

The clinical trial was completed over a three-

month period, between July and October of 1998. As the sponsor has earlier indicated, three system faults were experienced during surgery resulting in a 12-13 delay in two cases and a 20-minute delay in the third case.

The sponsor described that in all three cases the system responded in a fail-safe manner. The instruments stopped responding to surgeon input. The definition of fail-safe here is that the system entered the appropriate error-landing state without uncontrolled motion. This ensured patient safety and allowed the instrument to be removed safely. While the exact cause of the failures has not been determined, the sponsor was able to pinpoint the failures to an electronic board. A modification has been made to reduce the likelihood of future faults of this kind. In each case the system had to be restarted to complete the procedure. A second modification has been made to add a reset button to the interface panel that will reduce the time to restart the system and continue the procedure.

This concludes my presentation. I will return to review the panel questions after Dr. Horbowyj and Dr. Bushar have completed their presentations. I would now like to introduce Dr. Horbowyj.

Clinical Aspects

DR. HORBOWYJ: Good afternoon. My name is Roxi Horbowyj. I am a general critical care surgeon and the

clinical reviewer for this application.

[Slide]

So, I will be presenting the FDA clinical perspective on the Intuitive System's laparoscopic clinical study. A lot of the aspects have already been gone over in good detail by the sponsor and so I will really just go over highlights, including the objective, the design, procedures, endpoints, sample size determination, the target population, outcomes and end with a brief summary.

[Slide]

As you know, the Intuitive Surgical System allows surgical tasks to be performed with software-assisted three ports. Two are for the surgeon's hands and one is for the laparoscope. In conjunction also conventional laparoscopic instruments may be used for any additional ports or for any instruments that are not adapted to the system.

[Slide]

The objective of this study, as you have heard, was to demonstrate that the Intuitive surgical endoscopic instruments would be equivalent in safety and to standard laparoscopic equipment, which was in the control, when used to perform general laparoscopic tasks such as grasping, cutting, blunt and sharp dissection, approximation, ligation, electrocautery and suturing.

[Slide]

Taking these tasks into account, the design of the study was intended to provide valid scientific data that would allow reasonable clinical assessment of device safety and effectiveness, independent of the regulatory path to market.

So, the study was prospective, concurrently controlled, carried out by multiple investigators with single mask, and randomized, in this case preoperatively, after inclusion and exclusion criteria were met and informed consents were signed. Follow-up was for 30 days.

[Slide]

The procedures that were chosen had these surgical tasks in mind. Laparoscopic cholecystectomy was chosen because it is a well-established, widely practiced procedure, usually straightforward and it is excisional. So, any trauma caused to tissue would most likely not be seen in the patient as the tissue that is manipulated -- most in this procedure is removed from the patient.

Laparoscopic Nissen fundoplication was undertaken because it is technically more challenging, and it is a reconstructive procedure, therefore, any effects on tissue would most likely be retained within the patient and could possibly present sequelae.

[Slide]

Sample size was determined upon consideration of

multiple variables. We looked at the literature-reported complication rates with these procedures; the literature-reported cohort sizes; the sample size that might be needed for learning curve assessment, the sample size needed for clinically reasonable assessment of safety and effectiveness; as well as sample size that would be determined by statistical calculations.

[Slide]

The endpoints that were chosen were as much as possible endpoints that have been previously validated and were objective, and represented safety and effectiveness.

[Slide]

The endpoints, therefore, chosen by the sponsor were conversion rate were defined in the protocol as conversion of ISI to conventional instruments or conversion of control to open technique. It was recognized, and would be recognized, that patient anatomy and pathology, software or hardware failure, and surgeon or surgical team position on the learning curve could contribute to conversion.

Procedure duration was defined as being from skin incision to skin closure; postoperative hospital stay in days; DeMeester score at 30 days, specifically for laparoscopic Nissen fundoplication.

Quality of life was evaluated using the psychological well being score at 30 days, as well as

preoperatively. This score particularly has been used in gastrointestinal procedures in the past. It has been used evaluating Nissen fundoplication done both in the open technique and with laparoscopic technique.

Other measures of safety that we usually look at, such estimated blood loss, were considered, and then specific to these procedures would be bioleak and dysphagia.

[Slide]

The target population, as you heard described, were otherwise healthy adult patients with gallbladder disease or gastroesophageal reflux disease confirmed by this protocol, who were expected to benefit from non-emergent laparoscopic cholecystectomy or laparoscopic Nissen fundoplication, and who were willing to participate in a clinical study.

[Slide]

The outcomes can be looked at preoperatively, intraoperatively and postoperatively. Preoperative data shows, as the sponsor has shown, that the control and investigational device study populations were clinically comparable for demographics and inclusion and exclusion criteria.

[Slide]

Intraoperative data, such as review of video tapes, shows that laparoscopic cholecystectomy demonstrated

grasping, blunt dissection, cautery dissection, as well as suture placement around cystic duct and arteries.

Evaluation of knot integrity, as was mentioned earlier by one of the panel members, was precluded by conventional clip placement on the patient side of the cystic artery and duct.

As you have heard, two investigational device randomized patients were converted to and completed with control due to patient pathology and possibly because of surgical team position on the learning curve.

[Slide]

Similarly, for laparoscopic Nissen fundoplication video review demonstrated grasping, blunt dissection, cautery dissection, needle suture placement and suture tie for tissue approximation. As you have heard, one investigational device randomized patient was converted to and completed with open technique.

[Slide]

Looking at procedure duration and estimated blood loss has brought up some discussion. Looking at the means, for both procedures differences are seen, as well as in the standard deviation and the range. Similarly, there are some differences that are seen in estimated blood loss.

When looking at the data per investigator and comparing investigator to investigator, generally what I

have found was that there was variability per investigator as well as from investigator to investigator. There seemed to be more variability for the investigational device compared to control, and there seemed to be approximation of investigational device procedure duration to control with time or number of cases. But this pattern was variable and the degree of approximation to control varied from investigator to investigator.

[Slide]

This is an example which I hope will help to illustrate this. This is a single investigator who completed 57 cases. This includes his training cases. This slide shows both laparoscopic cholecystectomy as well as Nissen fundoplication for both device types used by this investigator. This investigator shows some of the points that I wanted to demonstrate but it is not necessarily the person who had the largest number of cases.

In the blue and the pink are the investigational device procedures. The triangles represent Nissen fundoplication and the circles being laparoscopic cholecystectomies. The yellow and the orange are control devices.

I think what this demonstrates most is the trends. There are variabilities in all but the controls for procedure duration are low and some are more constant

throughout the study. These cases are plotted in time as completed by the investigator. So this would have been his training case on laparoscopic cholecystectomy and this would have been his training case on Nissen fundoplication. These would have been his final two cases performed during the study. What you also see is that, for example with Nissen fundoplication performed with the investigational device, as time goes by, as he does more cases, the procedure duration time approximates control. You don't quite see that as much with laparoscopic cholecystectomy performed with the device, perhaps because there just were fewer cases performed by this investigator, and so we didn't see that approximation.

[Slide]

As you have heard, there were several unexpected events, three episodes of intraoperative software and hardware shutdown into safe mode during the middle of the clinical study. These did extend operative time 12-20 minutes, with no known patient sequelae. They were recovered, however, with active engineering intervention, and they required system and system use modification.

[Slide]

Further, outcomes in the postoperative time show that for control and investigational device study populations adverse events rates, quality of life at 30 days, DeMeester scores at 30 days and postoperative length

of hospital stay were clinically comparable.

[Slide]

In summary, the ability to perform surgical tasks with the investigational device and the control device in laparoscopic cholecystectomy and laparoscopic Nissen fundoplication has been demonstrated in the study population, specifically grasping, blunt dissection, cautery dissection, suture tie placement around tubular structures, needle suture placement and suture tie for tissue approximation. Notice, sharp dissection is not listed here.

[Slide]

Unexpected system shutdown into safe mode occurred requiring active engineering intervention and system as well as system use modification.

There was some increase in procedure duration and variability in estimated blood loss compared to control, and there were non-device failures associated with conversion of two investigational device randomized laparoscopic cholecystectomies to control device which were completed with control device, and this may be attributable to surgeon or surgical team position on the learning curve for the device use. There were no conversions due to device software or hardware failure during the study.

Thank you. Dr. Bushar will now present the statistical aspects of this study.

Statistical Aspects

DR. BUSHAR: Thank you, Dr. Horbowyj. My name is Harry Bushar. I did the statistical review of this submission. What I did is I actually entered the sponsor's data and did all of the statistical analyses that I thought were necessary. I also checked the sponsor's work and I deferred to the sponsor's results over mine. In no way do I differ with the sponsor on the technical analyses. The differences lie in the way I approached the data and the way I looked at the protocol. The main thing is that I took an intent-to-treat approach, which means I looked at all the patients. I didn't exclude anybody. They were randomized; they were in the study. Also, I didn't make any decision about what was or what was not to be included. If an event occurred and was reported, I used it in the analysis.

[Slide]

I did look at the clinical equivalence studies that the sponsor completed. These were the laparoscopic cholecystectomy, and I will refer to that as LC from now on, and the laparoscopic Nissen fundoplication, or LNF study.

The clinical trial design, as Dr. Horbowyj explained, was preoperatively randomized, patient masked, concurrently controlled by conventional laparoscopic instruments, and it was multi-investigator, that is, four surgical teams within one site in a hospital in Mexico City.

[Slide]

What I will be talking about here is mainly the statistical equivalence testing, which was promised in the protocol, and the objective of statistical equivalence testing is to show that the Intuitive group in this case is not worse than, that is better than or equal to the control group within delta, where delta is some positive value. The reason for that is that everything I am going to be measuring -- larger is worse. So, I am trying to show that Intuitive is not larger or not worse than control. To quote the sponsor, delta is qual to some predefined and clinically meaningful difference above which the two different methodologies are no longer considered to be substantially equivalent. This is sort of the essence of what I am talking about. I get into a lot of details but the main thing that the panel has to focus on is what is clinically relevant.

[Slide]

To put this in terms of equations, the statistical equivalence test hypotheses are -- well, the null hypothesis is what you are trying to reject because this means not equivalent. It means that the mean of the outcome for Intuitive is greater than or equal to the mean of the outcome for the control plus some delta.

The alternative hypothesis, which you would

achieve by rejecting the null hypothesis, is one of equivalence and that is just the opposite of what the first equation says, that the mean outcome of the Intuitive is now less than the mean outcome of the control plus some delta.

This is not just a matter of subtracting the means, which these hypotheses might seem to indicate. The means are from a sample and we are trying to project to the population. The delta applies to the population. That is why it is not a simple difference. You have to take the mean into consideration; you have to take the standard deviation and the sample size into consideration to actually perform this statistical test.

[Slide]

To begin, I will show you the clinical endpoints or deltas from the LC protocol table on page 387. What I have done, I have gone down the left-hand side of that table which says what the effectiveness outcomes and safety outcomes are, and down the right-hand column which says what the delta should be. This is not what the sponsor said was intended. There are different values in the text; there are different values in the footnotes, but I am going strictly with this table.

To begin with, with the primary effectiveness outcome the conversion rate had a delta of 3.5 percent. The secondary effectiveness outcomes consisted of two, the

procedure duration with a delta of 45 minutes, and hospital stay with a delta of 0.4 days. The safety outcome referred to overall complication rate. I am not leaving any complications out. I am not saying this is the best way to look at the data. This is one way to look at the data. This is what was stated in the protocol and that is what I a going to be covering. Here the delta is 3.5 percent, the same as it is for conversion rate.

[Slide]

If I apply that to the LC clinical findings and do the statistical test for equivalence, for the conversion rate there were two conversions in the Intuitive. So that gives me 3.5 percent mean for the Intuitive and a zero percent mean for the control. The predetermined delta is 3.5 percent. You don't even need a statistical test there. This is not equivalent. There is no way you can show that it is less than 3.5 percent.

However, the minimum delta that would just allow equivalence to be established, in other words, if you used the equations that the sponsor provided, you can back-calculate a delta of 7.5 percent, which means that if that were the delta you used, which was not, then you could conclude from this data, from this sample, that the difference was less than 7.5 percent.

This is a secondary analysis and something like

this really generates a new hypothesis which should be tested with the new studies. So, this is just a way of looking at how we interpret the data when it doesn't show what it was intended to show.

[Slide]

Moving on, for procedure duration we got 109 minutes in the Intuitive group and 67 minutes in the control group, with a predetermined delta of 45 minutes. This leads to non-equivalence. We can't reject the null hypothesis. However, the minimum delta that would just allow equivalence to be established is not much greater than that. You don't have to double it. You just add 6 minutes; you are up to 51 minutes. You can actually show from this data, if that were the delta, that the Intuitive-control difference would be expected to be less than 51 minutes in the population.

[Slide]

Continuing, the LC procedure duration learning curve, which has been mentioned and is presented in an analysis by the sponsor, Dr. Bloch did this using general estimating equations and he showed that the linear slope of the procedure duration curves is 0.69 minutes per procedure for Intuitive and 0.83 minutes per procedure for the control.

Now, the above reduction rates are not statistical different from zero so that the conjecture that learning

here would be expected to eventually catch up, in other words, Intuitive would eventually catch up with the control, does not appear to be plausible from this data. But it is going down. But I think the point here is that surgeons are getting better as they do more and more Intuitive operations; they are also getting better and better as they do more control operations within this clinical study.

[Slide]

The LC clinical findings with statistical test for equivalence for hospital stay -- here the hospital stay for Intuitive was 1.3 days and the hospital stay for control is 1.2 days. Even a predetermined delta as low as 0.4 leads to equivalence. There is equivalence there.

[Slide]

Going on now to safety, looking at the complication rate -- again, I am looking at all complications -- there is 3.6 percent in the Intuitive group and zero percent in the control group. The predetermined delta is 3.5 percent. We see that as not equivalent. However, if we boost that delta up to 7.7 percent we could just get equivalence.

[Slide]

Here is another variable that I looked at and the sponsor looked at also. This is the LC blood loss. This was not mentioned in the protocol but it was collected by

the sponsor and they did analyze it. The means were 19.2 ml for the Intuitive and 5.6 ml for the control, and this is statistical significantly different, with a very low p value. So, there is more blood loss on average in the Intuitive than in the control but whether or not 20 ml means anything is, of course, a matter of clinical interpretation.

[Slide]

Continuing now with the next study, the LNF, again I am beginning with the clinical endpoints, deltas, from the LNF protocol table on page 388. The primary effectiveness outcome is stated to be conversion rate, but then the sponsor goes on to discuss the DeMeester score, and I think the delta given there, 2.22, was meant to apply to the DeMeester score but I just used the same delta as for the previous study, 3.5 percent. I am not sure what was meant by what was in that table. Anyway, I am doing the same thing for this study that I did for the previous study when it comes to conversion rate.

For secondary effectiveness outcomes, the procedure duration is now slightly increased, from 45 to 50 minutes. The hospital stay, comparing LC to LNF, is now up from 0.4 to 0.5 days. For safety outcome, the overall complication rate, the delta here was doubled, from 3.5 to 7 percent. So, this is what the sponsor wrote in the table.

[Slide]

When I begin with procedure duration I see I get 137 minutes for the mean for the Intuitive and 89 minutes mean for the control. With a predetermined delta of 50 minutes this is not equivalent. However, I have to increase that by 13 minutes to just get equivalence.

[Slide]

Looking at the learning curve now, here things look a little bit different. The linear slopes, again using the sponsor's analysis for GEE, general estimating equations, you get the Intuitive reduction at 4.5 minutes per procedure and a control reduction at 2.1 minutes per procedure. These reduction rates are statistical significant so they really are coming down, but there is no statistically significant difference between Intuitive and control. Even though one is double the other, statistically they don't show up as being different. So, you may or may not conclude how easy it is going to be for Intuitive to catch up to control. Obviously, they are both coming down. They are eventually going to catch up to each other but we haven't seen beyond 19 procedures at most per surgeon. So, we really don't know where this is going but this looks good because the Intuitive is coming down apparently harder than the control.

[Slide]

To look at the hospital stay, here we get 1.4 days

for Intuitive and 3 days for the control. The predetermined delta of 0.5 days is not equivalent, and the reason for that anomaly, as the sponsor mentioned, is that there were two outliers in the control group which greatly inflated the variance. When I looked at this using non-parametrics I also got pretty much the same answer, and it would be possible to achieve equivalence by raising the minimum delta up to 0.93 days.

[Slide]

Going on to complication rate, here it was very high. This is all complications. It was 19 percent for Intuitive and 15 percent for control. The predetermined delta is 7 percent. This leads to the conclusion that this is not equivalent. The minimum delta that would just allow equivalence to be established is 15 percent.

Here I did something a little different. Another way to approach "what if" when you don't get to reject your null hypothesis is, well, suppose we want to get 19 percent Intuitive and 15 percent control, suppose we just raise the sample size and keep the delta. Well, the sample size would have to go through the roof before this would become equivalent. It would have to be 847.

So, the point of this is that if you try to do equivalence testing when the Intuitive is coming out slightly worse than the control it becomes a very difficult

task to do. In other words, it may be better to look at complication rates and conversion rates solely in terms of qualitatively looking at the rates and making sense out of it rather than trying to do a formal statistical analysis using equivalence testing.

[Slide]

Again, with the LNF blood loss, here it was very similar in numbers to what we saw with the LC, 18 ml for Intuitive and 9 ml for control. However, in this case it is not statistically significantly different.

[Slide]

As far as my conclusions go from the clinical study of statistical equivalence, with the one exception, that is the LC hospital stay, statistical equivalence was not demonstrated, using the clinical endpoints or deltas from the LC and LNF protocol tables.

Therefore, deltas may be increased, if clinically feasible to do so -- that is your decision -- or the sample sizes per group may be increased in an attempt to establish statistical equivalence.

That ends my presentation. I would like to turn the podium back over to Dwight Yen to provide the questions.

FDA Questions

MR. YEN: At this time, I would like to read the panel questions that were provided to the panel members back

in May. You also have a one-sheet summary of these questions in front of you.

Although not limited to these questions, these are the particular questions that we are asking for input from the panel during the panel deliberation following the presentation from the primary panel members. At that time we would be happy to clarify any additional issues that you may have.

The first question, please discuss what you consider are the benefits and the risks of this device for the intended use based on the preclinical and clinical performance data presented for laparoscopic cholecystectomy and laparoscopic Nissen fundoplication.

Question number two, please discuss whether or not you believe the net risk-benefit ratio adequately supports the use of this device for general laparoscopic surgeries.

Question number three, clinical use of this device during this study was limited to relatively healthy, adult patients, expected to benefit from elective LC and LNF procedures. Please discuss concerns, if any, regarding the use of this device in general surgical procedures in populations that may be vulnerable to increased blood loss and/or procedure duration associated with device use, for example, patients requiring emergent intervention, pediatric patients, elderly or small adults.

Question number four, the sponsor of this device has claimed that the device is fail-safe. That is, the device has adequate safeguards built into both the hardware and software such that any failure of the device during surgery will not introduce unacceptable risk to the patient or surgeon. Please discuss the adequacy of device fail-safe design for this intended use.

The last question, limited clinical experiences indicate that surgeons and surgical teams need to be properly trained to use this device. Please discuss the types of training that will be warranted to assure that the device will be safe and effective.

Thank you.

DR. WHALEN: Thank you, Mr. Yen. We will now have the panel deliberations and comments. As stated in the agenda, we will begin with three scheduled panel member presentations, which will include Dr. Hannaford on a technical overview of the PMA, followed by Dr. Talamini with a clinical overview, and ending with Dr. DeMets on the statistics of the submission. Dr. Hannaford?

Panel Deliberations

Preclinical Overview

DR. HANNAFORD: I really like using Power Point but it is still an immature technology and I am afraid to count on it for an important meeting. So, I went to Kinko's

last night and printed it out. Once you take a floppy disc to Kinko's I always destroy it because you get so many viruses at Kinko's. So, now I don't have a floppy to stick in your machine. So, I will just go with the old-fashioned system.

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This is my first panel session. I am just a consulting member of the panel, and what I have done is divided this talk into three segments. The first is a very generic overview of this technical area. In the second segment I am talking about the ISI system as I understand it from the material that I got, and not having the benefit of anything I have heard today, of course. The third section is sort of what I recommend as action. So, if you want you can stop me if this isn't the appropriate time for that since I don't quite know the protocol yet.

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This is an area which I think is new to medical devices but not new to technology, and it started in the Manhattan Project era when they had to handle very dangerous nuclear materials for building nuclear weapons, and they had to do dexterous things to them in order to shape them into bomb components.

So, they invented these mechanical teleoperators or through-the-wall devices, called waldos, as early as the

1940s. But these devices were characterized by a fully mechanical implementation. So, there was a mechanical link between the operator's hands and the manipulators on the other side.

But then, for a couple of reasons, it was advantageous to make that an electronic link instead of a mechanical link, for example, if you had to exceed a 15 ft distance or you had to have a moving relationship between the two sides. So, they developed them in an electronic form.

What you are seeing, I think, today is sort of a 1990s version of these systems which are still in wide use. Even the mechanical systems are still in wide use and work very well. Then, in research we saw the introduction of computers into these systems and now we are seeing telerobots controlled on the Internet in very beginning demonstrations.

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You heard the term bilateral, some of you did. This topic was discussed in the closed session in response to my questions. This is a well-known term; it is not a secret. This term falls into the class of bilateral teleoperators because it creates this virtual physical connection between, in this case, the surgeon and the patient's tissue.

Here are some technical issues in that kind of system that have to be addressed, and certainly have been in this product for the most part. Mechanical design has to be done very carefully to achieve those attributes so there is any chance of this force information passing back and forth in both directions.

The visual registration between the operator's hands and the motion of the robotics system is very important for performance.

Force feedback is very important as well, at least in some cases. When they initially remotely controlled these mechanical devices in the '50s or late '40s, it was a position only control. That was totally rejected by the operators because they didn't have any feel.

Now we are in a similar situation as open surgery converted, say, ten years ago to laparoscopic surgery. The surgeons have lost the ability to, say, palpate tissues and make certain kinds of discriminations.

Finally, a technical issue is control properties of this system. Because it is computer controlled or electronically controlled, what is the performance and the quality and stability of that system?

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To get more into control, bilateral control means a control system where there are two points where the system

interacts with the physical world, or ports is a term that can be used. Here, we are talking about the surgeon touching a handle at one end and the tool touching the patient's tissue at the other end. So, there is some kind of control equation buried in there, somewhere, that has two inputs, one from each of these ports, and two outports to each of these ports. If that is done properly it creates this virtual physical link. So, if I move the system until it comes into contact I should feel some force that stops contact.

I think it is interesting because I think we will see more -- as far as I know, this is the first commercial device employing this technology and I expect to see more of them in the future. But it is not something where there are established standards or protocols for validating performance and safety yet.

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What are some aspects of performance? Can the operator distinctly feel some contact with a soft or hard object? Does the operator feel impeded or damped or some kind of resistance when they are moving in free motion? When I move in real free motion I don't feel anything significant. Is the system free of vibration or oscillation? Is the force accurately controlled at the end effector when it comes in contact with something? And, what

is the force scale? In other words, what is the ratio of the surgeon's force to the tool force?

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Stability -- this is really the most challenging engineering area in these systems, and it is an emergent property of the entire system. You can't predict stability or analyze it without thinking about everything, including the surgeon's and the patient's biomechanical properties. So, it depends on all of these different things, and other ones.

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Generally speaking, unstable systems are unsafe because they are not responding to the surgeon's inputs; they are doing their own thing. But there are safety measures that do work. Instability is really a cause of the system, say, applying too much force or moving too fast. So, if you have a safety system which detects those conditions, that is a valid way to address those risks.

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The ISS system itself -- its name, as we have heard a couple of times, is an instrument control system, intended to assist in the accurate control of endoscopic instruments. But just to clarify, it is not an assist in the sense of power steering on your car where you have a mechanical link to the steering gear and a power assist.

This is something different from that because there is no physical link in between.

It certainly is intended to follow the surgeon's motions and commands and, to some extent, to couple the response of the body back to the surgeon, but it controls all the energy flow into and out of the surgical tool. I am thinking of mechanical energy here, force, displacement and their product.

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This is sort of a simplified bock diagram abstracted out of the block diagrams that I have seen. The point is that this is the surgeon's side. There is a mechanism that contains motors and sensors. The motors are capable of pushing back on the surgeon, and the sensors can detect the surgeon's motion. Then, there are similar things over here, on the patient side, actuators, meaning motors that can drive the instrument in all its different directions and sensors which measure what the instrument is doing, and there is redundancy in these for safety. But the key thing is these are connected not by any physical link but by the computer's hardware and software.

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I would classify that as a bilateral impedance-controlled, force-reflecting teleoperator. Again, this is based not on complete information but what I have in the

distribution. The worst case for stability -- as I pointed out, the stability of this system depends on what it is in contact with and sometimes, for some architectures, the worst case will be when it is in contact with something rigid. For other architectures it is when the system is in free motion. So, this is not a pejorative term about this system; it is just how you have to analyze it for stability. That case is when both sides are free. The best case is when both sides are touching something or are constrained by something. Each possible architecture has a worst case and best case. Again, this is not either pro or against the system we are talking about today.

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I guess I will continue then with what I think about the system and recommend for this panel. First of all, there is the issue of level of concern -- again, I am new to this area but from what I read, it applies primarily to the software, or exclusively to the software part of the system, and some of the documents, I guess, are hand-me-downs from the previous filing so they mention the lowest level of concern but, clearly, just to "disambiguate" that, and I think that is the case here, as we change from blunt tools to sharp tools the same amount of physical energy can do a lot more damage. So, I agree that a concern of moderate is warranted.

Again, I think in principle the system could with those sharp tools do a lot of damage but I think that the level of concern applies to software only. The hardware in the system is a good check on the software, as I understand it. So, I think describing the level of concern of software as moderate makes sense here.

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Issues that I have -- first of all, in looking at the videos I thought I saw instances of instability, and I certainly have not done any careful, exhaustive study of a large sample of material but I did see cases where I saw the end-effector -- not on all the tapes -- vibrating and that gives me a concern.

Kind of along with that, there is really very little documentation at all about the control system in what I have seen. So that gives me a concern. That includes the gain-stability margins, instances of instability, and even specifications analysis or testing is completely absent. Now, this may have to do with proprietary information but I think that is a concern.

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These are some things I would like to see documented on the system, namely the control equations, or at least the nature of the inputs and outputs used in the control; the stability analysis; analysis of the worst case

loads for stability; the maximum stable gains. These are technical things but I really think what you are seeing here is a brand-new introduction of technology into surgery. Of course, I am very excited about it. I agree with the statements that the sponsor has made about the future potential of this system. So, I think it is in everybody's interest to document this first foothold of a very important new technology.

Then, the gain values that are used in production compared to, say, this maximum stable gain. The other two important related features are tremor filtering and scaling, which are mentioned with literally about three words in the filing but not documented in any detail. For example, what frequencies are passed through and what frequencies are attenuated when tremor is filtered by the system.

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Finally, the questions -- I really don't have any expertise pertaining to the first three questions so I will just confine it to questions four and five. I think the system does show --

DR. WHALEN: Dr. Hannaford, forgive me for interrupting but we are going to ask for each panel member to make comments upon the questions as they come up.

DR. HANNAFORD: Fine. In that case I am finished.

DR. WHALEN: Thank you very much. Dr. Talamini?

Clinical Overview

DR. TALAMINI: My name is Mark Talamini, Associate Professor at Johns Hopkins, and this is a non-statistician, non-engineer viewpoint of what I had before me to look at before this meeting. I am an active clinical surgeon. I do about 300 cases a year. About half are laparoscopic, advanced laparoscopic, and about half are open. So, I am not a laparoscopic evangelist for these kinds of technologies. On the other hand, my primary research interest is in the physiology of this type of surgery.

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A lot of what I put together for this is already brief but I will make it briefer because I think it now falls into the category of beating a dead horse. We have already talked about advantages of laparoscopic surgery. I think they are clear and well-documented, both in surgeons' experience, patients' experience and in the literature at this stage.

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We have talked today already also about the disadvantages of laparoscopic surgery, the things that are taken away when surgeons are operating in this fashion. As has been alluded to, there are substantial things that surgeons give up when they do this type of surgery.

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In terms of the two procedures that were studied and have been talked about a lot today, again I will give you the general surgeon's perspective. A laparoscopic cholecystectomy, quite frankly, is a pretty easy operation to do. That is the reason that this operation was introduced in this country in late 1989 or 1990, but by 1992 three-quarters of the cholecystectomies done in the State of Maryland were being done this way. Think about that. The entire general surgery work force trained to do this operation in two years. So that tells you two things: It tells you that it is a pretty easy operation and that surgeons are pretty adaptable.

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Laparoscopic Nissen is different. The laparoscopic cholecystectomy is an exterpative operation. You are taking something out so there are things to ligate, things to divide. The Nissen is a different operation. It is more difficult technically. It takes a longer period of time. It is a reconstructive operation where the surgeon is required to rearrange tissues so it takes a different set of skills, a different level of skills. Because of that, the potential complications are more substantial. I think it is good that we have information for both of these types of procedures to look at today because they are different, and they look at different aspects of surgery.

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The whole idea of computer-assisted or robotics in surgery is an interesting one. On this slide I have put down some ideas that do not pertain specifically to the application for today but to this whole field in general. Those are that laparoscopic surgery really is ideal for the application of this sort of thing, high technology applications, for a number of reasons. It depends on the image stream and that image stream can be digitized, manipulated and altered. Information can be added to it. But, really, the promise for us, surgeons, is that high technology would not replace us but enhance what we do.

Now, the HMOs might like to replace us. There might be a cheaper alternative, I don't know. But we believe really that the promise is that as we move forward and apply technology, that is out there in other industries, to what we do, we will be able to do things better than we do them now. In the liver we will be able to see where blood vessels are beneath the surface of the liver, even though they can't be felt or observed in any other way. The idea of being able to tell what type of tissue might be tumor and what type is not by using different ways of evaluating the surfaces of those tissues, force feedback.

Telemedicine I think is a controversial area because I don't know of any patient of mine or one here, in

Gaithersburg, that would like to have their surgeon other than at the operating room table. But it has been an area of growth, and certainly one published in the literature, and it is one that the military is very interested in.

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In terms of the current application and, again, I don't want to beat a dead horse because all of these issues have been alluded to and I think we are about to discuss them, the learning curve effect is important and it sounds like, from our presentation so far, there are at least two different ways to look at the learning curve effect with this application. The experience of laparoscopic cholecystectomy is an important one in that surgeons did learn that technology fairly quickly.

The blood loss aspect, again, I think it is significant but we are talking about very small levels of blood loss. I was surprised that in the study the investigators were actually able to measure blood losses that small given these types of procedures. It is very difficult for me at the end of an operation to know if I have less than 50 cc of blood loss, let alone discriminate between 10 and 20 or 30. So, it does appear that there is a significant difference between the control groups and the study groups but it is at a level that has me scratching my head a little bit as a clinical surgeon.

The complication rates and, again, we have already talked about this -- are certain complication rates more pertinent in evaluating this than others? The investigators have certainly given their opinions on which are more important and which are not.

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This part is not beating a dead horse. This is what I think is new for me as a surgeon. For me, in evaluating the mass of material that was sent to my office, the video data was by far the most important. That is probably because as a surgeon that is what I do every day. So, in looking at those videos I could think about and experience what I do every day.

I think the statistical analysis and the study obviously is important and it is meant to do a certain thing, but for me to see exactly what surgeons were able to accomplish during operations was extremely important.

I have summarized here what I thought I saw this system able to accomplish, and I looked at many hours of videotapes, more than I think the rest of the panel was able to. The system did have the ability to make quite precise motions, and I saw in a number of instances that the surgeons were able to pick a target, very, very small, and go in and exactly pick it up or precisely manipulate it, to my eye, more effectively than I usually can do with a

chopstick instrument at a 1.5 ft distance.

I also was impressed in a number of instances, when bleeding did occur during these operations with this system, that the surgeon was able to take this instrument and very precisely grab right where that blood vessel was and control that bleeding, which again left me scratching my head a little bit about the differences in the statistical analysis for blood loss because on the videos, it seemed to me, most of the time the surgeons were able to very precisely control bleeding.

Also, despite the issue of force feedback, I think the strategy of giving very good visualization and good magnification and three-dimensional vision allow the surgeons to very gently dissect tissues, in my view, looking at these videos.

I thought they were able to tie the knots very effectively. There were some videos where I saw the sutures slip just a little bit, others where I didn't see that and I imagine there may have been some technical changes from one to the other in the design of the instruments or the settings in terms of the amount of pressure they were putting. But, certainly, in some the knots were nice and tight and there was no slippage; in others there was a little bit of slippage -- not slippage of the knot itself but slippage of the grasper on the suture. But I could see

that the surgeon recognized that and worked to make sure that the knot was still tight despite that.

Finally, the other thing that I saw that I think is perhaps the power of the system from the surgeon's point of view is the similarity of this system to actual hand motions. Of course, that is because of the multiple degrees of freedom.

That is all I have from a formal point of view. From a surgeon's perspective, the other point that I would make is about this whole issue of training. I want to just make two points in terms of training. One is the laparoscopic cholecystectomy experience. You know, lap chole was never exposed to a randomized, prospective trial. I think general surgeons were actually fairly lucky in that it turned out to be a safer, better operation because that whole thing happened so fast that nobody really ever had the time to do an important randomized, prospective trial which, of course, is the gold standard for all of us, clinicians.

Despite that, surgeons learned the procedure and, with the exception of some increase in complications, that has really been a success story for general surgery, yet, it was not legislated. There was no committee saying, yes, you can do this or, no, you can't do that.

So, I have that on the one hand of my experience history. On the other hand of my experience history I have

the whole laser thing. Remember, when we started laparoscopic cholecystectomy it was called laser laparoscopic cholecystectomy, oftentimes primarily for marketing. The laser turned out not to be very effective, in fact, perhaps dangerous in some instances, and that was device based. So, that was a different situation. I don't understand what was going on with the FDA at that point. I think these were all already approved devices being used for cholecystectomies.

So, I am not quite sure in my own mind yet where to put this application in that experience of mine, with lap chole on the one hand, which worked out very well, and the laser application, which was the use of a device with that operation that I think did not work out so well and has now fallen by the wayside. So, I offer you those as my thoughts. Thanks.

DR. WHALEN: Thank you, Dr. Talamini. The final scheduled presentation, Dr. DeMets on the statistical overview.

Statistical Overview

DR. DEMETS: Thank you. I am going to have a very low tech presentation, and a very brief presentation, partly because I was heading out the door on a week-long trip when Dr. Krause tipped me off that I might have to make some remarks. So, I have resorted to the low tech approach.

What I thought I would do is spend a little time trying to set the stage for the panel about this active control equivalence business because I think it is something that either gives you a headache or makes you glassy eyed a little bit.

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First of all, let me say it is a very challenging problem. Statisticians have spent most of their time thinking about how researchers detect differences, find differences, and the process that we are talking about is somewhat different than that. There is not a lot of literature on it and there is not a single agreed upon way to do this, although I will have a suggestion.

One of the things that happens to you is that things get reversed. If you think about superiority trials, which is what we typically are thinking about, versus non-inferiority or maybe equivalence, the process gets reversed. Let me try to explain it very simply. Dr. Bushar got to it just a little bit. In the typical situation you have a null hypothesis of no difference in event rates, or mean values, or something, and you have an alternative hypothesis where you are trying to detect some size difference and you power your trial to detect that. That is the usual process we go through.

In the active control versus experimental

situation or the equivalence you are flipping things around. The null hypothesis is that, in fact, there is a difference of a certain size; that the two treatments differ by some amount. I call that delta minimum, and I want to come back to that. What you are trying to do is establish that, in fact, the difference that exists is less than that delta. That is whey the delta business is floating throughout the discussion of today.

In either case of superiority or equivalence you have to have a large enough study to detect the differences that you think are important. The size of that difference is not a statistical question; it is a clinical question, a clinical decision question. It has nothing to do with statistics. How you determine it and how you detect it and rule it out is a statistical problem. So, I guess, that is point number one.

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Two is in the material and even, in some ways, in the discussion today. There has been some back and forth about what scale of reference do we use. In fact, throughout the FDA these days there are several pockets of discussion going on, whether it is devices or whether it is drugs or biologics -- I don't know about devices so much, but there is no agreed upon scale of reference.

What do I mean by that? Well, regardless of

whether it is binomial, or yes or no, or success or failure outcome or some continuous variable, one can express those differences as either an absolute difference, absolute difference in rates, absolute difference in events or measurements, or on a relative scale, such as a relative risk, the ratio of the success rates or the failure rates, or percent of change relative to the control arm. It doesn't really matter which scale we choose. It doesn't matter whether it is continuous or binomial. But we probably some day, within this panel or the FDA in general, should kind of try and get some consensus whether the language is conducted in English or in French because that is really all that is involved here -- what language, which scale do we want to talk about so we are not confusing each other every time we pick up a different variable.

The fourth point is that to think about this kind of a problem you have to specify what I call the minimum delta. What size delta for a particular variable -- and you have to remember which variable and what kind of scale, absolute or relative, and that is how you express the delta -- do you think is minimally of clinical interest? In other words, where would you walk away from the process thinking it doesn't matter to me? That is a clinical decision that you have to figure out. It doesn't depend so much on statistical issues at this point, and that is a key issue.

So some of the discussion that was presented by the FDA review had to do with what difference was stated versus what we could have detected, and the presentation by the sponsor also alluded to that a little bit.

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The only way that I can keep my thoughts straight about this whole process is reflected best in a paper that Tom Fleming wrote almost ten years ago, when we were debating and discussing AIDS trials, but it is very generic methodology. I was disappointed in the presentation this morning because I thought, based on what you handed out, you came very close to this method.

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Let me try and explain this picture, which is the only thing I had time to xerox before I walked out the door. I think it is a very simple, clear way to think about what is on the table for our discussion. In the classical setting -- and I am doing this on a ratio, a relative scale. This is a figure from Tom Fleming's article. So, 100 percent on the scale says that the two treatments have absolutely the same effect, whether it is event rates, failure rates, success rates or measurements. What you want to do is to show that the difference that you observe, which in his little example was 125 percent, plus or minus two standard errors actually exceed delta. That would give you

a significant result, with a p value less than 0.05.

So, this is the confidence interval. It excludes 100 percent. You say, well, we are better than that. So, we have an improvement. If we don't have a confidence interval that excludes 100 percent or a ratio of 1, you say we can't rule out that they are the same. So, we can't claim superiority.

In our setting, remember, we are flipped around. We are down here. So, here 100 percent says that the two therapies are exactly equal and we don't want to be worse than that by very much. That is this delta minimum. So, there is some delta below the 100 percent that we will pick. And, he has it sitting right here in his diagram. Of course, there is an opposite side delta which is not so interesting for the discussion here.

So, if you do a study, do the confidence interval, and in this case the lower limit of the confidence interval is above that delta minimum, you have ruled out that you could be worse off by this much or below. You have ruled out you are not worse than the standard you set and, in fact, you are even a little bit better than that. On the other hand, this confidence limit includes that delta. So, you haven't ruled out that you could be that much worse.

So, this is a very simple, comfortable approach that expresses the data you got, and by looking at that

confidence interval you can see what is in and what is out. What have you ruled out and what can't you rule out?

Then you say, okay, what delta did I really care about? Where do I clinically walk away from this? Thus, I would say if there is anything that is converging as a point of view among biostatisticians that I hang out with, this approach is seemingly where we are heading. The reason I was disappointed in the presentation this morning was that in the materials handed out to us, not presented but handed out, there are confidence intervals for the experimental group and the control arm and you can see the variability and the overlap and what you can rule out. It is not expressed as differences, which is what I prefer, but at least it is expressed in terms of confidence intervals.

That is kind of how I sort of think about this. So, the presentations about what delta are we arguing about really has to do with what you think is clinically important. The way this process should go, in my opinion, is that you should say what is the question, and what measurement are you going to use for that question, and what scale. What is clinically relevant? Select the scale in which you are going to present things. Select the delta minimum that, again, is based on clinical considerations, not statistical. Size your trial accordingly so you can detect that minimum. Present your results in this

confidence interval approach, and then say do I rule out the delta minimum that I a priori specified, which presumably has some clinical relevance, and you can make your decision whether you make your case.

I was somewhat curious, and perhaps that could be clarified, that the sample size for this study seems to have been said in advance at 50 per arm, without a lot of consideration of what is the question. And, the deltas are sometimes specified and sometimes not. So, I am a little unclear about that.

I think that the issue about counting all patients in studies is one that we settled long ago. That is, you have to account for all patients that you entered, and to try, as tempting as it might seem, to talk your way out that some patients didn't sort of fit the criteria has a problem which was alluded to earlier. That is, if you get rid of all the tough cases then, of course, things get better. This debate in the surgical community took place intensely in the CABG debates about the patients who didn't get CABG shouldn't be counted. Well, okay, if you get rid of all the sick patients then, of course, I am going to look better. We have been through that debate and I think we have convinced ourselves that it is very difficult -- you don't have comparability anymore and you cannot call it a randomized trial.

My final comment is that the learning curve, based on the data I observed, seems to be longer than being in Mexico City for one day and then the real stuff the next day, even though I know surgeons are very adaptable. If you look at the data, it takes ten to twelve, to twenty patients before the data starts settling down. So, perhaps another comment on this design is that the learning curve for the experiment that we have seen wasn't long enough.

But my main point is to go back to the way you think about the data that you have before you, which is to look at what delta is of clinical value and importance to you. So, I would actually draw your attention in the discussion to what was not presented today, and maybe the sponsor could pull those slides up. But that is how I tried to sort this out. It is a tough problem. If you are having trouble with this as a clinician, don't worry; the statisticians have also been having trouble addressing this problem.

That is all I have for formal remarks.

DR. WHALEN: Thank you, Dr. DeMets. Before the panel tackles the first question, as promised this morning, this is the opportunity that the panelists have to ask questions either of the sponsor or of the FDA if, indeed, any of those questions linger. Dr. Burns?

DR. BURNS: I have a question about exactly what

it is that we are reviewing for approval. Are we looking at the instruments as well as the system for approval? Is that all part of the system?

DR. WITTEN: I am not sure what your question is.

DR. BURNS: Well, there are instruments that are used with the system, and those are not standard laparoscopic instruments, as I understand it.

DR. WITTEN: It is the instruments plus the indication change from the already cleared part of the product.

DR. BURNS: So, under approval it is the instruments that would go with the system.

DR. WITTEN: Well, it is the system plus the indication that they now want. They presented what the indication was they have and what indication they want. So, it is the system plus the indication.

DR. WALKER: I guess we still haven't heard the answer to the question we are both asking, which is no tests were done on harmonic scalpels. Are we being asked to approve the harmonic scalpel as a factor of this device today, or will you come back to the FDA later for harmonic scalpels? Can the sponsor enumerate for us the factors that we are being asked to approve today?

DR. MOLL: I wish we had that list back up. There were some very specific tools to accomplish electrocautery,

graspers, needle drivers, scissors, and that it.

DR. WALKER: No scalpels of any kind?

DR. TALAMINI: It says sharp endoscopic dissectors, scissors, scalpels, forceps --

DR. MOLL: The added new instruments are forceps, scissors, scalpels, clip appliers, needle holders and electrocautery.

DR. WALKER: But scalpels here excludes harmonic scalpels.

DR. MOLL: Yes, absolutely.

MS. DUBLER: And it is my understanding that you are asking for approval for those instruments for the purposes discussed today.

DR. MOLL: I believe that is correct. It is approval of the instruments for the stated purpose of using them in laparoscopic surgery.

MS. DUBLER: So, if you wanted to use these same instruments for cardiac surgery you would feel compelled to come back to the FDA.

DR. MOLL: Correct.

DR. FERGUSON: I am impressed with the restoration of the surgical skills that this device might provide surgeons after we have been struggling with chopsticks, as he says, for a number of years. But my question is why does it take so much longer since all surgeons have learned those

skills when they were learning to be surgeons. Why does it take that much longer to do the cases when we have now forces applied that have been returned to us, and the ability to use scissors and so on?

DR. MOLL: Well, I think Dr. Gardiner attempted to address that, and we believe that the surgeon is given more dexterity but he is also given a new surgical tool, and with that tool and that system comes other types of new things that they need to learn about and be comfortable with. Like with any surgical device, there is training involved and a learning curve.

DR. FERGUSON: That doesn't answer my question. I am sorry.

DR. GARDINER: I think that we see on both sides of the study learning going on. Having been one of the four people that did the surgery, I felt I was, to some degree, learning again. I was using a new assistant, and I got better as I went along in doing the conventional laparoscopic that I had done thousands of times. I was using a new assistant who was unfamiliar to me, and I was using different instruments in a different location. So, there is learning that was going on, actually, on both arms of this study.

With regard specifically to the Intuitive device, you are learning a couple of things. There is learning that

is going on in terms of how to drive this system, how to operate with it, how does the surgeon actually use the console. That is one aspect of the learning. There is also learning that is going on in terms of how the assistant interacts with the device and the patient, and how the assistant and the surgeon interact together. And, I think that those factors together make this a little bit slower, and I think it is going to get better and faster as we get more experience. It certainly has with every other laparoscopic procedure I have done.

DR. FERGUSON: I guess what I am looking for -- I am not trying to be pejorative about it but I am looking for the positive fact that if you give surgeons back their surgical skills that is a good thing.

DR. GARDINER: Well, having sat down at this console and operated, and then going to the control patients and operating, there is no question, all four of us by the end of the study, when the card would get pulled up and we saw we had to do a control case, every one of us said, "oh, gee, I'd rather do this with the Intuitive system." Every one of us felt that way.

I think if you look at it and say what would I rather have? Would I rather have a more dexterous instrument or a less dexterous instrument; a more flexible instrument or a less flexible instrument; a more accurate

and precise one or a less accurate and precise one, as Dr. Talamini raised, you know, in the videos, I think we would all take the more capable equipment every time.

DR. TALAMINI: I really don't want to sound like an advocate but I don't think speed is always the end-all and be-all. One of Halstead's great contributions was to say, look, we can slow down and do things better. So, there certainly can be instances where a different technology that takes more time is superior to a quicker technology. I am not saying that is the case here but we need to have our minds open to that possibility I think.

DR. GARDINER: Having been responsible for doing a lot of these operations, I can tell you that was exactly going on. There is no question about it. We certainly didn't feel in a race and we weren't in a race. We were taking our time.

DR. CRITTENDEN: I am still troubled though with the fact that this should be better because it has an articulated wrist but if you look at some of the data that the FDA compiled, the person who did the most study laparoscopic cholecystectomies never really approached the conventional time, and these are people, by your own admission, who were the most advanced laparoscopic surgeons available. So, I just wonder if you turn this over to someone who is coming out of their residency how they are

going to be able to adapt to this technology.

What is more, we have only looked at laparoscopic cholecystectomies which, by the panel's acknowledgment and by your acknowledgment, are pretty easy procedures. But now we are talking about potentially doing laparoscopic splenectomies and colectomies as well, and I wonder whether we should not just limit it to laparoscopic cholecystectomies and Nissens because that is what we have data for.

DR. GARDINER: I don't believe that the intent of the FDA was to regulate this device procedure by procedure, and I think there is some element of physician judgment and surgeon judgment that comes into play here. Beyond that, I am not sure how much further to go.

This is certainly more capable than a straightforward conventional laparoscopic tool. Does a lap chole show that? Really not. But you can see it in the suturing part of the Nissen, for example. I guess the worry I would have -- and I am kind of editorializing here and maybe I ought to sit down but, you know, you take this device and hold it back from a surgeon that could use it perfectly and wonderfully to do a common-duct exploration, for example, and suture the duct closed but hold that back because we haven't demonstrated that. I think that the equipment is highly capable of that kind of procedure, and

whether this is going to be capable or would be something you would use for a splenectomy is questionable. I think that really kind of goes to surgical judgment.

DR. WHALEN: Correct me if I am wrong, Dr. Witten, but we are discussing efficacy and safety with lap choles and lap Nissens. That is what the panel is charged to do. Correct?

DR. WITTEN: No, actually -- can you put up your indication statement? Maybe we could ask the sponsor to put up their proposed indication statement.

DR. TALAMINI: While you are doing that, if I could just ask one other thing, Dr. Gardiner, in the control lap choles did you tie the cystic duct or not?

DR. GARDINER: I am sorry, I didn't hear you.

DR. TALAMINI: In the control lap choles did you clip and tie the cystic ducts or did you just clip them?

DR. GARDINER: No, we did them both the same way.

DR. TALAMINI: So you tied them as well with the control lap choles?

DR. GARDINER: Right.

DR. HANNAFORD: This is also for Dr. Gardiner. Sorry to make you jump up and down. For us, non-surgeons -- actually, this is a question for any other surgeon in the room as well, can you give me an idea of the rate of trocar injuries in normal endoscopic lap chole? You had a certain

set number of them in the control arm, and what is the typical rate for those injuries in the normal operation?

DR. GARDINER: It would be significantly below one percent. I mean, we talked about that earlier this morning. It is hard for me to understand where those came from. I mean, we are not talking about surgeons that are inexperienced. They don't have that kind of experience in their own practice. We observed two of them.

DR. TALAMINI: There should be 1 in 500 or 1 in 1000.

DR. GARDINER: Yes, right.

DR. CHANG: Dr. Gardiner, again with due respect, I want to revisit one other question since if I were to present this as a proposal to our surgical OR suite to say this is a wonderful new instrument, there would be a cost-benefit analysis. Based on your data, how could we present how this system benefits the patient undergoing lap chole or lap Nissen fundoplication?

DR. GARDINER: Well, I think that in the lap chole you have an operation which is well established to be able to be done now with conventional instruments, and I don't think it is going to benefit the lap chole. You know, that was put up there and put in the study primarily to evaluate the use of this device in a basic operation, and that is what that does. How much capability this system is going to

provide to the surgeon I think is going to be answered over time. We may well find out, for example, that you put this piece of equipment in the hands of that resident that is coming out and you may well see that the resident that is given back more capability can operate better, faster and more efficiently because he or she does have capability that they can use, whereas the highly experienced surgeon may have been able to get around a lot of the limitations of conventional laparoscopy.

DR. WHITE: A real quick response, the cost-benefit analysis is way too early to approach at this time. We went through that same argument with laparoscopic cholecystectomy, subsequently laparoscopic Nissen and, frankly, every procedure out there and there are still some of them where that is an argument. Not universally but very significantly, over time the cost-benefit analysis has become known in these procedures. For this technology it is way too early to enter into that.

But most importantly, we picked lap chole and lap Nissen because, one, they are commonly done by the individuals involved but allowed us to use the device to do all these things we have listed up here. We could have included other operations but these were the ones that we could universally use frequently and often, and demonstrate the capabilities of this device. How that is going to

figure into the cost-benefit analysis is way too early.

DR. WHALEN: The slide that the sponsor is projecting, requested by Dr. Witten, makes me stand corrected. It generically says laparoscopic procedures, just to point that out.

DR. FERGUSON: I really need a clarification about what we are voting on here because I came in with the idea that we are approving surgical instruments, the ones that are listed here, for any operation that they might wish to do with this new device. Yet, I hear them saying that they are going to bring back coronary bypass at another time where they can use these same instruments.

DR. GARDINER: No, what we are dealing with is laparoscopic indications, indications in the abdomen, not in the chest.

DR. FERGUSON: Could I ask then why does the request not limit itself to those two operations because you can use all of these surgical instruments to do a coronary bypass if you wished to do so.

DR. DILLARD: If I might be recognized, Dr. Whalen?

DR. WHALEN: Yes.

DR. DILLARD: This is Jim Dillard from the Food and Drug Administration. I think that is an issue that is important to talk a little bit about. Let me come from the

FDA perspective about how we handle indications for use and how we look at the various types of data.

Obviously from the FDA perspective, we regulate the medical device and we regulate the labeling and what the labeling says. Where we tend not to get too involved is in the practice of medicine. So, what we are asking you to do here today, and this is from our perspective and where we come from, is that we do not want to be looking at newer technology procedure by procedure, disease state by disease state to try to approve devices as they become validated in each individual type of operative procedure.

From this perspective, we tried to look at very representative general surgical kinds of procedures, picked a couple that would be representative of how the device would be used, would stress the system adequately so that we would get an understanding of the various types of instrumentation, and really from our perspective looking at this, we would be saying, since we will ultimately have to send a letter of whether we approve it or whether we not approve it, that if we approve it, it would be for these particular kinds of instruments, in this case the way the intended use is written, for a laparoscopic surgical kind of a procedure, but we would also be very specific in the labeling about the kinds of studies and the kinds of data and the two models that we had that went into the

approvability of the product in that labeling situation.

We would not be saying, nor would we endorse if the manufacturer went out and started promoting the device for thoracoscopic, minimally invasive cardiac surgical procedures. We would say you are beyond the scope of your labeling; we did not approve that in the labeling. So, if the manufacturer wants to specifically state they can be used in other surgical procedures or in other surgical subspecialties, and they want that to be approved on the labeling the expectation is that they would present more data to us that we would then look at. Does that help?

DR. FERGUSON: Very much.

DR. DILLARD: Good.

DR. WHALEN: Other questions?

MS. DUBLER: I just want to follow-up on one discussion and the cost-benefit analysis is the basis for it. We have talked about individual benefit, and there is a school of ethical analysis these days that argues the following: that it is, in fact, unethical to approve new technologies that will add to the cost of medicine, given the number of people without health insurance and access to health care, unless there is a measurable benefit that proceeds from that technology.

Now, I think we have been told that we can't assess that benefit at this point, and we can't produce the

cost-benefit analysis, but I would simply like to register my discomfort that we may be adding a substantial cost without commensurate benefit.

DR. WITTEN: I would like to make a comment from the FDA perspective. I think these are very important issues but from our perspective at the FDA in terms of what we are obligated to do to look at device approval for a device, it is to look at safety and effectiveness of the product. Although I think these questions about cost certainly are important, I don't think this is probably the place where we are going to hash them out since we don't really require the cost information as a part of the application from the sponsor for device approval.

FDA Questions

DR. WHALEN: Thank you. I would like to thank the sponsors for being in a position to answer those questions. We are about to embrace the questions that are put to the panel by the FDA. The questions have already been read into the record, and they will be projected as we encounter them so I will not reread them.

The process that we will follow is this, each member of the panel is going to be asked to comment upon the particular question. I will, in staggered fashion, start with a different individual each time so you won't be left as the twelfth person to try to say the same thing in a

different way every time. Please do not feel absolutely obligated to articulate words if they are only a rehashing of what has already been said. A simple "I agree" would be appreciated by anyone who has a flight in the next three hours, I am sure. But if you have something important to say, please, by all means, say it.

Following everyone's opportunity to comment, I will attempt to distill the consensus into a precise couple of sentences. The sponsor will then have the opportunity to make any comment upon that. I will then ask Dr. Witten, a as representative of the FDA, if what we have collectively stated satisfies the FDA.

That being said, we will now embrace the first question, which will shortly be projected, and, briefly, has to do with benefits and risks in lap chole and lap Nissen fundoplication. I will ask for comments of the panelists, and since we had started introductions with Dr. Burns, I will ask first Ms. Brinkman for any comments.

MS. BRINKMAN: Well, I certainly believe that these instruments will enhance our ability to do laparoscopic surgeries and, certainly, laparoscopic surgeries have demonstrated reduced patient morbidity. It is a new technology. I think it is exciting, and I feel that we are moving forward and I am very supportive of adding the addition of these instruments.

DR. WHALEN: Dr. DeMets?

DR. DEMETS: Well, I am waffling a bit on this question because I don't think that the primary question as stated was really adequately addressed because of the size of the study. If you have a study with failure rates as low as these are, there is just no way you can definitively sort that out with 50 patients an arm, even though it is very encouraging in terms of the estimates. But you would have known that in the design phase. I mean, you would have some sense of what your failure rate is for standard laparoscopy.

So you then go to the secondary questions that were listed, and some make the criterion and some don't. When you start looking at changes of size of 2 or larger, not being a surgeon, those sound large to me but they may not be clinically important, and I haven't heard any discussion around the panel as to what the minimum delta is. That is the key for me. Have you met that criteria? I don't know. I can't judge that surgically. But clearly from the criteria that have been bounced around, it is marginal. Some do; some don't, depending on where you draw the line. So, I am not convinced.

DR. WHALEN: Dr. Ferguson?

DR. FERGUSON: I respect those concerns and have those too, but I agree with Ms. Brinkman about the overall package.

DR. WHALEN: Dr. Hannaford?

DR. HANNAFORD: I just want to add to the discussion that when thinking about benefits, which are mentioned up there, I think there are benefits -- well, I think we should be able to consider potential benefits, and benefits that may accrue in the future when some extension to this is approved.

DR. WHALEN: Dr. Galandiuk?

DR. GALANDIUK: I think questions number one and two almost could be combined, and I agree with Dr. DeMets about the delta being defined. Depending on what variable they look at, the device clearly isn't identical because it does take longer. Is that clinically significant? I don't think so. So, in other words, it may be different but none of these differences are significant, and I think it has been shown both to be safe and effectiveness.

DR. WHALEN: Dr. Crittenden?

DR. CRITTENDEN: I am having a hard time with the question because I am not sure there has really been a benefit that has been established, but I do think they are equivalent technologies. So, as best I can answer the question, I kind of agree with what Dr. Ferguson and Ms. Brinkman said.

DR. WHALEN: Dr. Anderson?

DR. ANDERSON: I agree. I think this is a

valuable technology. The four variables were conversion rate, procedure duration, learning curve and hospital stay. Of those, the procedure duration of 51 minutes was a non-significant delta. I think that that is an acceptable difference, particularly for a new procedure. I was satisfied with the learning curve data which, because it looks like other learning curves that we see, such as in sentinel node mapping, and I think this is very promising. I am supportive.

DR. WHALEN: Dr. Chang?

DR. CHANG: In thinking about risks versus benefits, it appears that the major risks and the untoward events that occurred during the conduct of this clinical study was actually due to low tech instruments, such as the trocar and other instruments not related to the Intuitive system such as the harmonic scalpel. Those would be another issue related to just laparoscopic surgery in general and the risks for patient populations. So, I feel that this exciting technology is worthwhile in putting on the market.

DR. WHALEN: Dr. Talamini?

DR. TALAMINI: In short, I think the benefits to outweigh the risks for the device. I think the increased length in operative time is statistically significant but not important clinically, and I think the same in terms of blood loss. I think the benefits are that some day I will be

able to do my whipple using these types of tools.

DR. WHALEN: Ms. Dubler?

MS. DUBLER: I don't think we have heard sufficient discussion of benefits to be able to address number one. In regard to number two, my concern is the following: That in order to arrive at a positive risk-benefit ratio not only do we need more data on benefit, but I fear we need more data on risk, which would be related in my mind to the dimension of the training that will be required. People who are not sufficiently trained could, in fact, pose a risk using this procedure. Therefore, I think both of these questions have yet to be adequately addressed, whereas, I think that the notion of equivalence lets us address the safe and effective issue I don't think it lets us address the ratio issue.

DR. WHALEN: Dr. Walker?

DR. WALKER: Let me put in my two cents worth for what I see the benefit of this product to be. Clearly, the risks are about the same so we don't need to go into that. The numerator part, however, is that we are being asked to evaluate -- if we look at your ethics question, is there an ethical benefit? And my answer is, yes, there is a very real ethical benefit because this is an enabling technology. This is a first step to something that will have really far-reaching benefits for the patients. I agree that in this

particular application no benefit has been shown. But if we quash and don't approve, then that second step which really shows the promise will never be allowed to be taken by this company. So, I think we have a moral obligation, as long as they are safe and effective, to say go for it and show us the real benefit in step two now that we have given you permission in step one.

DR. WHALEN: Dr. Burns?

DR. BURNS: I pretty much concur with Dr. Walker. I feel this is an important first step. In an absolute sense, there perhaps hasn't been an enhanced benefit shown over standard laparoscopic procedures but, listening to the panel presentation as well as the investigators, it appears that it is at least equivalent, or can be equivalent, and potentially is an important first step into things that could potentially be much more beneficial in the future.

DR. WHALEN: I would summarize that the panel feels that the data has largely demonstrated, with some asterisks about its numeric versus clinical significance, that this is a safe and effective technology and, furthermore, that the preponderance of opinion would say that there is a net risk-benefit ratio in its favor, with an important disclaimer on the ethical side of things on our ethics expert.

Are there any comments in that regard from the

sponsor?

MR. DANIEL: No.

DR. WHALEN: Dr. Witten, with that consensus, has that successfully answered both questions one and two?

DR. WITTEN: Yes, thank you.

DR. WHALEN: Thank you. We will go to question number three which, as many may recall, is the lengthiest of the five questions, and has to do with some extensions into other arenas. Staggering again, we will start with Dr. DeMets.

DR. DEMETS: Not being a surgeon, I will pass.

DR. WHALEN: Dr. Ferguson?

DR. FERGUSON: Given some of the answers I got a minute ago, I don't think this falls within the purview of the group to concern itself with in the approval of this particular device. What is going to happen is that everybody in the room knows that this is going to be applied widely across all kinds of surgeries and all disciplines, and it will be inevitably misapplied, unfortunately, in some situations. I look on our job here, today, to regulate not number three but number five. So, I will hold off on that.

DR. WHALEN: Dr. Hannaford?

DR. HANNAFORD: I also will pass, not being a clinical person.

DR. WHALEN: Dr. Galandiuk, you can't pass because

you are a clinical person.

[Laughter]

DR. GALANDIUK: I don't really think it is relevant because it is the same issue as if you are doing an open operation. There is going to be a difference in tissue strength and fragility of tissues whether you are operating on a 90-year old woman or a 20-year old ma, and the same will be true for this technique. So, it is not any different than conventional surgery.

DR. WHALEN: Dr. Crittenden?

DR. CRITTENDEN: I agree with this. This is a purely clinical decision and I think really is beyond the purview of the panel to really talk about, and I think the surgeon on the scene has to make their own decision about this based on the clinical data they have at hand.

DR. WHALEN: Dr. Anderson?

DR. ANDERSON: I agree. This is a clinical decision. Bad decisions are made at all levels, not just with new technology, and this is not unique.

DR. WHALEN: Dr. Chang?

DR. CHANG: I would ditto. Once this is on the market, we really are dependent on clinicians' judgment in the proper use of the instrument.

DR. WHALEN: Dr. Talamini?

DR. TALAMINI: I agree with Dr. Ferguson and the

rest.

DR. WHALEN: Dr. Dubler?

MS. DUBLER: Pass.

DR. WHALEN: Dr. Walker obviously passes. Dr. Burns?

DR. BURNS: I agree in that any potential misuse can only be guarded against by the appropriate labeling and good judgment by the surgeons.

DR. WHALEN: Ms. Brinkman?

MS. BRINKMAN: I agree. Unfortunately, mistakes will be made but we will learn.

DR. WHALEN: So to be very concise, Dr. Witten, I would say that this falls under the practice of medicine in the opinion of the panel. Are there any comments by the sponsor?

MR. DANIEL: No.

DR. WHALEN: Does that satisfactorily answer the question?

DR. WITTEN: Yes.

DR. WHALEN: Thank you. Going to question number four then, it has to do with the device being labeled or claimed to be fail-safe. I will start this one with Dr. Ferguson.

DR. FERGUSON: I think this is one of the strongest aspects of the whole proposal, to me. I think the

way in which the company has approached the potential problems that could occur with complex machinery of this type is outstanding.

DR. WHALEN: I will ask Dr. Hannaford to disambiguate this issue for us a little bit --

[Laughter]

DR. HANNAFORD: Well, I generally share that opinion. My concerns about stability are more like something that, for the most part, are a potential cause of a failure, not so much a failure of fail-safe. In other words, there are these hardware mechanisms that are well documented in the filing which will catch this kind of failure, should it occur.

In the trial there were three instances of that happening. I was a little concerned at first when I read that the threshold for that failure detection was raised in response to those three failures. The instance in particular was a current check which, after a certain period of time, caused a fault if the current exceeded a certain value, just like a circuit breaker in your house. But, in detail, the time interval required to trip that safety feature was set to be extremely short, a few hundred nanoseconds, as I recall, which is a very, very, very conservative setting and one that is very likely to be triggered by non-dangerous, noise type of events. So, it

didn't bother me at all that they something like doubled that time. In fact, that almost is evidence of how well the safety features seemed to be working. So, I basically concur.

One other slight concern I would have is I wonder about if there are any effects of hardware failures on stability of the system. In other words, are there failure modes which could cause the control system to go unstable?

So, I am sort of a one-note person here, but this is where my expertise comes in. We built a similar system in the lab, much less sophisticated, of course, but we had an instance where if a cable was not tight enough -- if the cable became loose the system could go unstable. So, that kind of thing should at least be thought about, anyway.

DR. WHALEN: Dr. Galandiuk?

DR. GALANDIUK: Well, I have to defer to the experts.

DR. WHALEN: Dr. Crittenden?

DR. CRITTENDEN: I don't have much to add but just kind of wonder since this is an enabling technology whether or not some sort of objective performance criteria ought to be set in regards to the things that Dr. Hannaford talked about during his review. That is all I have.

DR. WHALEN: Dr. Anderson:

DR. ANDERSON: The safety concerns about the

software crashing was what I understood to be the major problem, and I don't put that in the same category as the device, you know, moving wildly and injuring a structure. There are lots of reasons that things can slow down in the OR, including the nurse not having the right equipment for you or the wrong cart being pulled. This happens all the time. I think that the safety mechanisms are fine for this.

DR. WHALEN: Dr. Chang?

DR. CHANG: I think the answer is yes.

DR. WHALEN: Dr. Talamini?

DR. TALAMINI: I am a little surprised at the word fail-safe. I have learned through painful experience to never say "never" or never say "always" in surgery because you are always being proven wrong. But I think the system, as I see it, is at least as fail-safe as my tired resident who is helping me do the case.

[Laughter]

I would feel better about it if I had used it five or ten times and felt how you can actually swing things out of the way quickly, but it seems from the videos and the data that that capability certainly exists.

DR. WHALEN: Dr. Dubler?

MS. DUBLER: Pass.

DR. WHALEN: Dr. Walker?

DR. WALKER: The term fail-safe bothers me as well

because it brings up visions of the Titanic and Dr. Strangelove.

[Laughter]

And, I would hope that the sponsor doesn't actually say their device is fail-safe but, rather, points to the adequate safeguards of it.

I share Dr. Hannaford's concern about the hardware failures and the myriad of possibilities for instability that that could lead to, but I feel reasonably comfortable that the existence of the product problem reporting system to FDA is going to mean that if those problems they can't be swept under the carpet and they will have to be dealt with.

DR. WHALEN: Dr. Burns?

DR. BURNS: I have to defer to Dr. Hannaford for some of his comments, but it would appear, based on what we have seen, that the system is fairly safe. I would look forward to the sponsor being able to respond to Dr. Hannaford's concerns.

DR. WHALEN: Ms. Brinkman?

MS. BRINKMAN: I just want to emphasize the fact that we remember to provide good technical training. I don't understand at all, but I am always sure that there is some good technician that does.

DR. WHALEN: Dr. DeMets?

DR. DEMETS: Computers fail, and they fail more

often because of software -- glitches in the system, than they do hardware, at least in my experience. And, I don't know how you would do it but I am not so confident that the software is fool-proof. I don't know how this division tests software, but I suspect that there are holes in that software that some day some realization will occur that we haven't anticipated, and goodness knows what the results would be.

DR. WHALEN: Dr. Witten, with the important caveat echoed by several members that nothing is a hundred percent and we wouldn't label this as totally fail-safe, I believe I can represent the consensus of the panel that we do feel that there is adequate safety built into the system.

Any specific questions from the sponsor or any other comments that someone would like to address?

DR. GOODHART: There were a couple of questions, most of them center around stability and on the issue stability analysis, we have done complete analysis in several different frames and, in fact, very much the terms that you presented in your summary. The FDA should have those. We are happy to provide additional detail in that sense. We have observed no instability in the system in any of its operative modes.

You brought up a second issue on stability, which is failure -- how did things fail. In fact, you brought up

a specific example of a cable. On our systems we have redundant sensing. Redundant sensing is on either side of cable drives. So, if we do see, for example, the thing that you mentioned -- a cable go loose -- we can detect it in advance of tip motion and transition to fail-safe.

So, we have done an analysis of how this failure affects stability as a whole, and that is a consistent set of performance evaluation tests that we do at every product release interval.

You had mentioned scaling, filtering and things like that, we do have performance criteria and performance tests available at the FDA, and in additional detail, if necessary.

On the software front, we do exhaustive testing. We also rely very heavily on following standard software procedures. One of the biggest things we want to make sure we do with our software is exercise every single mode that the system can get into, and we do that exhaustively. You had mentioned a specific concern of kind of an unexercised raffle that you never quite get into, and one of the things that we do is make sure that we hit every raffle that the system can head for. So, to the best of our ability, we addressed that concern.

DR. WHALEN: Do any panelists have any follow-up comments or questions?

DR. HANNAFORD: Yes, I will follow-up. I guess that pretty much satisfies me because my main desire was that the control design is well documented in the FDA just because it is really introducing a new thing and something that I think is going to show up in other devices, other areas, other companies -- and, just so that it is done right. That is my main thing. It just isn't in the material that I saw in advance of the meeting.

DR. WHALEN: Dr. Witten, does FDA feel that question four has been adequately addressed?

DR. WITTEN: Yes, thanks.

DR. WHALEN: Thank you. The fifth and final question has to do with training issues, and I will first ask that Dr. Hannaford make comment.

DR. HANNAFORD: My one point on the training -- actually, I have two points on the training. One is that there is some very recent data from collaborators of mine at UW on training using some simple simulators, and then evaluating performance of those students in their further clinical training with animal surgery and human surgery. They found that their initial study showed no effect. Then they realized that the learning curve was, in fact, longer than they expected. Once they extended the number of training repetitions out to around nine repetitions, then they were able to measure, in a statistically valid way, the

effects of the training.

So, I think the number of operations required is on the order of ten or more to see that kind of training effect. Of course, this was a little different. This was residents or beginning surgeons. The authors of that study would be Dieter Pohl and Mika Sinanan.

The other thing is I think a training program for this device ought to cover the exceptional cases. So, the surgeons ought to be explicitly trained about failure modes or system fail-safe modes -- what the surgeon should do when X happens, even if that is a very unlikely thing. That is one of the benefits. In fact, just for the future I see a tremendous benefit related to training because ultimately you will unplug the console from the robot and plug it into a computer, and the surgeon will practice on a computer simulation. Again, that is not what we are seeing today but that is where this can go. So, I think there is a lot of benefit for training ultimately to this technology.

DR. WHALEN: Dr. Galandiuk?

DR. GALANDIUK: I agree that training has to be very clearly specified, not only for the operating surgeon but also for the nurse or technician in the operating room that will help. I was looking at the user manual here, and the control panel has five pages of terms and pictures on it. To me, that looks intimidating, and I think it would be

very important to ensure that anyone who purchased this device in terms of hospital -- whoever was going to be the technical advice person in the operating room go through all this and be very familiar with it.

Similarly, I think there should be a requirement in terms of hours that a surgeon trains for this. The surgeons are all, you know, "we know everything all the time, you know, just look at this and browse through this and be comfortable with it," but I think that with this you should require a certain amount of both didactic as well as animal lab or simulation training to "certify" surgeons for this because it still is different from regular laparoscopic surgery and I think it would be important to ensure safety on the part of the surgeon doing this rather than just the device.

DR. WHALEN: Dr. Crittenden?

DR. CRITTENDEN: I would echo those remarks. I don't have anything to add.

DR. WHALEN: Dr. Anderson?

DR. ANDERSON: The training I think is the most important part of what was discussed today, and I just want to make the point to the sponsors, echoing what Dr. Talamini said, with laparoscopic cholecystectomy we were lucky. We went up to a one percent common duct injury rate but because the operation was so much better we survived that. But in

this setting, this isn't that much better than standard laparoscopy and I think to protect your device for the future we really need to make sure that this is adequate, and very specific non-human practicing needs to be done because this is really a different technology.

DR. WHALEN: Dr. Chang?

DR. CHANG: Laparoscopic cholecystectomy is patient driven. There is no doubt about that. I mean, it just exploded because patients asked their surgeons for the mini-procedure, and so I would echo all the comments that physician education would be key in terms of success in advancing this instrument.

DR. WHALEN: Dr. Talamini?

DR. TALAMINI: Training and credentialing were the sticky wickets of laparoscopic cholecystectomy, and they are still being wrestled with for laparoscopic procedures. The issues are complex -- who pays for the training? How are surgeons going to take time off for the training? It is not simple and straightforward. Whose responsibility is it? Who decides when somebody can do this and when not? So, I don't think it is a simple issue but it is an awfully important issue, and I think it is important for this device because this is the first device where the surgeon affecting tissue manipulation is distant from the patient's tissue.

So, I would even propose that we ask the sponsor

to development some sort of a formal plan or proposal as part of the approval process. Being a novice, I don't know how that works but I think it is an important enough and a difficult enough issue that it warrants that much attention.

DR. WHALEN: Dr. Dubler?

MS. DUBLER: I think these are very helpful comments, and I too would be inclined to approve the technology subsequent to a training program or certification program being suggested by the sponsor. I don't know what analogous situations we might turn to for guidance. Perhaps there are some; perhaps it really is a matter of first impression. But, I think if we take the patient in this complex seriously and the patient is being asked to balance and choose between different technologies, the training of the person who is performing and using this new technology will determine the risk. If patients are to address for themselves the question of their own values and a risk-benefit ratio, then I think in fact there has to be a level of certification and training that becomes the base for patient choice.

So, I think I would like the sponsor to be able to tell us how they think this could be done, and I would be inclined to build that into the approval.

DR. WHALEN: Dr. Walker?

DR. WALKER: I am very uncomfortable with the

notion of an FDA regulatory mandate for a certain number of hours or a certain type of training, and would argue that that should not be a condition of approval. The reason is that if there are patient injuries from untrained surgeons using this device, then the sponsor is going to be the deep-pocket co-defendant sitting in court with the surgeon, and I think that probably is going to have the effect of ensuring adequate training before the device is sold, probably a better program of adequate training than we, sitting here as non-training experts today, could possibly come up with.

DR. WHALEN: Dr. Burns?

DR. BURNS: I agree that training for the surgeon as well as the surgical team is going to be important for this. I don't know if I would make that a requisite for approval, other than to note that it should be worked out between the sponsor and the FDA upon approval.

DR. WHALEN: Ms. Brinkman?

MS. BRINKMAN: If I were you, I would develop the hottest video game and get it in every doctor's lounge, and I bet you there is a high correlation between people who are good at video games and people who are good at this kind of surgery --

[Laughter]

-- and all of us who don't have that eye-hand coordination will probably never be very good at it. So,

make it fun and they will be doing it just for the fun of it and they will learn well.

DR. WHALEN: Dr. DeMets?

DR. DEMETS: Well, as I pointed out in my comments, I think it does take more than two or three cases to get the learning curve over with, and the data that has been submitted show that, I think. How you translate that into regulatory language, if at all, I don't know.

DR. WHALEN: Dr. Ferguson?

DR. FERGUSON: I agree basically with what has been said, particularly with Dr. Burns. I don't think it ought to be part of our charge to tell them how to train. I think the company will be responsible for that. I do think that in that analysis you have to carry it a long way past just the surgeon who is being trained but think about resident training and all of the problems that we have had with VATs technology and trying to teach residents in hospitals how to do it when there is sort of only one person who can be doing something on time. So, there are a lot of those issues that are going to come up for the future.

The other comment I would like to make is that, again looking at the future, I don't know how you do this but I would like to be assured somehow that the surgeon who is responsible for the case is in the room, and not removed to another tele-situation, and also that he was able to get

to the patient and get in, in case of a severe emergency. You are not going to see that in what we have been talking about today, but you can see it a lot in cardiovascular procedures. So, looking toward the future there, I think that it would be worthwhile thinking about those. Those are not on the table today, of course.

DR. WHALEN: Dr. Anderson has one more comment.

DR. ANDERSON: The question of should the FDA be telling this group how they should be teaching, I don't think that was the proposal that Dr. Talamini suggested. The question was to ask the group, you tell us how it is that you would have these people taught. The four surgeons who did this work know more about what this procedure is like than anyone else in the world, and they can design for you, I think, a protocol that looks reasonable. And, I think it is important to document that, that this is how it ought to be done, not to say you have to do eight of them and then you are done. We want to hear from you more than what was said today about how you would teach them.

DR. WHALEN: Dr. Witten, in answering question number five about the types of training that the panel feels are warranted, in summary, it should cover any failure modes that are inherent in the system. It should cover the entire operative team and not simply the operating surgeon. There should be didactic portions followed by either inanimate or

animal laboratory sessions prior to use in humans. There should be a formal plan or proposal as a component of the sponsor's application. And, there is discomfort in specifying any specifics as to the number of hours that would be entailed.

Are there any comments by the sponsor?

DR. MOLL: I just wanted to remark that Intuitive Surgical takes training very seriously. In fact, we believe it is one of the keys to both clinical and commercial success. I would also like to agree with a couple of very insightful comments that training and the methods of training will change over time, and we believe one of the really exciting parts of this technology is not only now it can impact the practice of surgery clinically but how it can affect clinical training.

MR. DANIEL: On behalf of Intuitive Surgical, I would like to thank the panel and FDA for a very thorough and thoughtful analysis. Thank you very much.

DR. WHALEN: Dr. Witten, does FDA feel that question five has been adequately addressed?

DR. WITTEN: Yes.

DR. WHALEN: Thank you. At this juncture, as mentioned this morning, we do have a second opportunity for any public comment that wishes to be made. Is there anyone in the audience who wishes to make comment at this time?

Seeing no hands being raised, we can proceed to summations. Is there any final comment from FDA?

DR. WITTEN: No. No, I think we have said everything we have to say.

DR. WHALEN: Thank you. Is there any final comment from the sponsor?

MR. DANIEL: No.

Concluding Panel Deliberations and Vote

DR. WHALEN: Thank you. We will then proceed to voting, and I would remind everyone that the industry and consumer representatives do not participate in the voting. I will only vote in the case of a tie. Dr. Krause will read the voting instructions for the panel.

DR. KRAUSE: Everybody here in the audience and the panel, we all get to be the first ones for these new voting instructions. They used to be two pages; they are now one. So, we get to try it out here today.

The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by

applicable publicly available information.

Safety is defined in the Act as reasonable assurance, based on valid scientific evidence that the probable benefits to health, under conditions on intended use, outweigh any probable risks.

Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended uses and conditions of use, when labeled, will provide clinically significant results.

Your recommendation options for the vote are as follows: Option number one, approval -- you can vote approval with no conditions attached.

Option number two, approvable with conditions -- the panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the panel.

Number three, not approvable -- the panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe, or if a reasonable assurance has not been given that a device is effective under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Following the voting, the chair will ask each

panel member to present a brief statement outlining the reasons for their vote.

DR. WHALEN: Thank you, Dr. Krause. The chair will entertain a motion. Dr. Anderson?

DR. ANDERSON: I have a motion that conditions for approval, if one were to vote for conditions, would be that the sponsors supply a training description -- what is considered standard training by your group.

DR. WHALEN: The motion has been made to approve with conditions as specified. Is there a second?

[Seconded]

The motion has been made and seconded. Since we have brought up conditions, we can now discuss those conditions before proceeding to a vote. Please raise your hand if you wish to discuss.

DR. CRITTENDEN: I would like to add to the motion, and that goes with product labeling, that we ought to label this as being an equivalent product, not one that has clinical benefit, and that the clip applier was not clinically tested, and that the surgeon ought to be appropriately gowned.

DR. WHALEN: Restated then as approval with conditions, the conditions would be that the manufacturer have a training program created; that it be labeled as an equivalent program; that the clip applier not be within the

approval as it has not been tested; and that the surgeon be sterile and gowned at the time of the operation of the instrument. Further discussion of those conditions in the approval?

DR. TALAMINI: Could you just state that again for me?

DR. WHALEN: Probably not but I will give it a whirl. It is to approve with conditions. The conditions include the outline of a training program as proposed by Dr. Anderson; that there be labeling of it as an equivalent product; that the clip applier not be a part of the approved instruments; and that the surgeon be sterile and gowned when operating at the console.

DR. CHANG: Is this an amendment to Dr. Anderson's original motion?

DR. WHALEN: Well, if we are within Roberts Rules of Order we would have to regard it as such, so it would require a second. Is there a second to the further additional conditions of approval?

DR. HANNAFORD: Second.

DR. WHALEN: It has been made and seconded. It is open for discussion.

DR. TALAMINI: I feel as if we may need to discuss this training. I think we are asking for what would be a best-case training protocol on the part of the sponsor.

Would you agree with that, Dr. Anderson?

DR. ANDERSON: Yes.

DR. WHALEN: Further comments?

DR. HANNAFORD: Yes, can you explain what a best-case training protocol is to me? My questions about training are is it within the scope of the FDA's actions -- Can the FDA require a certain amount of training before this device can be used, or could one option be that the company can design a training program but that any user is required to follow that training program? What are the regulatory options for training?

DR. WITTEN: Maybe I can comment on that and if I am wrong maybe, Jim, you can jump in. We can certainly require that a sponsor design and provide a training program. But, as Jim already said, we don't regulate the practice of medicine so I think it would be unusual for us to require specific training for the individual user. That is, to have the training available is one thing but to require the training from the user would be, I think, beyond the scope of what we do.

DR. KRAUSE: Can I just read the approvable with conditions again? A panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education. So, it is definitely within the purview of the panel to recommend physician education.

MS. DUBLER: I think it is important to state that even though the FDA doesn't regulate practice, it is very powerful legally and morally for the company to say this is the program that the team has to undergo before the team is qualified to use this technology. So, I think that is very important and I hope the company would be comfortable developing it, given the fact that they are the only ones that have the expertise.

DR. WALKER: When we say with this addition or amendment that it be labeled as an equivalent device, legally what does that mean?

DR. WITTEN: Well, maybe I will give a more general answer, which is when we look at the panel recommendations we interpret what the panel is recommending in terms of what we can do. So, that might translate into, for example, providing the results of a clinical study on the label, which we would typically do in any case for a PMA. In describing the results in the label, you know, we might make the point that we think could be demonstrated by the study.

DR. FERGUSON: I have a little problem with that aspect. I thought we were headed on a track to talk about training but the words "equivalent device," to me, could be misinterpreted. There is no other device like this that I know of. So, when we say "equivalent device" what does that

mean? That means to us that they didn't prove superiority over the standard procedure. Is that not correct?

DR. WHALEN: Dr. Crittenden, would you answer?

DR. CRITTENDEN: Yes, it is not better than the conventional technique. So, I guess my particular concern is just that someone will market themselves as being a robotics surgeon and, hence, that is going to be better surgery, where it has not been demonstrated to be better but certainly equivalent.

DR. FERGUSON: I couldn't agree with that more, but when you say "equivalent device" I think that could be misconstrued perhaps.

DR. WHALEN: Other comments or questions? Dr. Galandiuk?

DR. GALANDIUK: I think we are putting too many conditions on this. I think the physician education is important, but whether or not the surgeon is gowned and sterile when he is operating with these controls I think is clinical judgment and should be left to the surgeon's discretion. Again, I think the mention of equivalency -- equivalence means different things to different people. So, I don't think I would make that a condition of approval.

DR. WHALEN: If my Roberts Rules are correct, we will first vote on the amendment, which are those additional stipulations which Dr. Crittenden has brought up, before we

will vote on the original recommendation which has the training within it. Further comments? Dr. Burns?

DR. BURNS: In regards to Dr. Crittenden's comment that it would be equivalent but not better, that is already implied in the existing label in the sense that it would be approved for laparoscopic surgery, period. It is not saying anything about it being better than any other procedure; just that it would be approved for that type of surgical procedure. So, I think it is implicit in the label as it stands.

DR. CRITTENDEN: I think that fair-minded individuals would agree with you but, given the marketplace and other incentives, I just wonder if there is some role for mischief.

DR. WHALEN: The chair would suggest that if somebody is going to put an ad in the "Boston Globe" and suggest that there is something or other, they are going to do it, not matter what the FDA and the sponsor does.

MS. BRINKMAN: Could not the dressing of the physician, to be sterile, be included in the education portion of it rather than just added on? It seems like if you get a good, comprehensive education package -- and my assumption is that it is to the company's benefit to do that anyhow, they could put that in as part of the educational process and say why.

DR. WHALEN: Further question or comment?

[No response]

We are first voting then upon the Crittenden amendment to the proposal, which has the three sub-elements within it of equivalence, clip applier, sterilely gowned and gloved.

All those in favor, please raise their hands.

[One hand raised]

Dr. Crittenden votes for. All those opposed, please raise their hands.

[Show of hands]

Dr. DeMets, Dr. Ferguson, Dr. Galandiuk, Dr. Hannaford, Dr. Anderson, Dr. Chang, Dr. Talamini, Dr. Dubler and Dr. Walker. The amendment is defeated. Is there any subcomponent of that amendment that wishes to be re-proposed as an amendment before we go to the original question? Dr. Walker?

DR. WALKER: I reintroduce the clip applier because that has not fully been shown to have been tested.

DR. WHALEN: Is there a second to that amendment?

[Seconded]

DR. WALKER: But perhaps that can be done between FDA and the manufacturer rather than involving the panel.

DR. WHALEN: The amendment has been made and seconded. Perhaps I jumped in prematurely, but we did make

and second it. Is there any further discussion of that? Dr. Dubler?

MS. DUBLER: I don't understand what the implications of the amendment versus the FDA doing it are.

DR. WHALEN: Well, as I understand it, we are approving a list of instruments. On that list of instruments was a clip applier. When the motion was originally amended it was pointed out that there had not been demonstration and testing of this, and that is why it was suggested that it be subtracted from the list. And, that I believe -- I don't want to speak for you, Dr. Walker, is why it has been reintroduced and seconded.

DR. CHANG: Could we have clarification from the FDA? That was my question earlier to the sponsor, that the clip was not tested. So, I asked if it were to be developed in the future would that be submitted to FDA as an amendment to their PMA.

DR. WITTEN: Any instruments that aren't approved as part of this PMA would need to be submitted as supplements to the PMA.

DR. CHANG: So, there is a protocol to be followed if the sponsor wants to introduce a clip applier.

DR. WITTEN: If there is anything that is not part of this approval, then they would need to supply the information separately.

DR. FERGUSON: Does that include the harmonic scalpel?

DR. WITTEN: Yes.

DR. WHALEN: Any further questions or comments to be made? Dr. Dubler?

MS. DUBLER: Is it appropriate to ask the sponsor a question?

DR. WHALEN: I don't know whether the protocol dictates it but it is fine with me. So go for it.

MS. DUBLER: Why is this on the list with other things that were tested?

DR. WHALEN: Any of the sponsor wish to answer?

MR. DANIEL: As I thought we indicated, but let me clarify, the clip applier that we had available was a small clip applier, not something that a general laparoscopic surgeon would generally use. We did use our small clip three or four times to clip a cystic artery.

DR. WHALEN: Seeing no further questions or comments, the panel is now asked to vote upon the amendment which is to subtract from approval with conditions approval of the clip applier. Will those in favor of subtracting that clip applier please signify by raising their hand and leaving their hand raised?

[Show of hands]

DR. WHALEN: That vote is unanimous. Is there any

further question or comment upon the motion to approve with conditions of training? Seeing no further question or comment --

DR. HANNAFORD: Question, sorry. Just the word "training?" What is the exact amendment or condition that we are voting on?

DR. WHALEN: Dr. Anderson, would you care to restate?

DR. ANDERSON: The proposal is that the condition for the sponsor is that they provide a detailed description of the training program which they recommend and endorse for the use of their product.

DR. WHALEN: Is there any further question or comment?

[No response]

The panel is then asked to vote upon the motion of approval with conditions, the conditions being that the sponsor provide a detailed training program which they endorse, and also, as amended, that the clip applier is not a part of the approval. Would those in favor of that please signify by raising their hands?

[Show of hands]

It is not unanimous so I will read the names: Dr. Ferguson, Dr. Hannaford, Dr. Galandiuk, Dr. Crittenden, Dr. Anderson, Dr. Chang, Dr. Talamini, Dr. Dubler, and Dr.

Walker.

Will those not in favor, those oppose, please raise their hands?

[One hand raised]

That is Dr. DeMets. It is approved. The recommendation of the panel is that the premarket approval application for Intuitive Surgical endoscopic instrument control system and Intuitive Surgical endoscopic instruments from Intuitive Surgical Inc. be recommended for approval with conditions, those conditions being that the sponsor will provide a detailed training program which they endorse, and that it not be labeled for use with the clip applier.

DR. WITTEN: Maybe you were about to do this but don't we need to go around and have them state --

DR. WHALEN: That is what I am about to do, yes, ma'am. With that recommendation being made, if each of the panel members who have voted please indicate why they have so voted. Just for giggles at this last part of the afternoon, we will go to Dr. Walker first.

DR. WALKER: I voted as I did because it seems to be a safe, well designed product and I am convinced that the sponsor has done its homework adequately.

DR. WHALEN: Dr. Dubler?

MS. DUBLER: I voted as I did because I think the safety and effectiveness of the product has been

demonstrated and because I am not permitted, according to the rules of the FDA, to take into account that it will add substantially to the cost of surgery.

DR. WHALEN: Dr. Talamini?

DR. TALAMINI: I voted affirmatively because I believe it to be safe and effective based on the studies done and the video case histories that were provided to me, but believe that the training issues are important.

DR. WHALEN: Dr. Chang?

DR. CHANG: I voted yes because safety and effectiveness was demonstrated. The statistical differences between the two study groups were not clinically significant. Again, as I know the sponsor has said, teaching and training for safe use is a primary concern of theirs?

DR. WHALEN: Dr. Anderson?

DR. ANDERSON: I voted yes because I think this is a great product, and I have nothing to add beyond what the other panelists said.

DR. WHALEN: Dr. Crittenden?

DR. CRITTENDEN: I voted in the affirmative because I think this is a safe and effective product in well-trained individuals.

DR. WHALEN: Dr. Galandiuk?

DR. GALANDIUK: I also believe it is safe and

effective, and the differences that were shown were not clinically significant, and agree with Dr. Talamini that I think this will add greatly to the agility of the surgeon performing laparoscopic procedures.

DR. WHALEN: Dr. Hannaford?

DR. HANNAFORD: I voted yes because I thought they showed it was safe and effective, and also demonstrated a lot of potential for future enhancements to surgery.

DR. WHALEN: Dr. Ferguson?

DR. FERGUSON: I voted yes for the same reasons, and I particularly like the concept of what is coming down the road.

DR. WHALEN: So, to keep them in their pews until the last hymn is sung, we want to go to you, Dr. DeMets, and find out why you voted against.

DR. DEMETS: Despite my enthusiasm and interest in the product, I don't feel that the data presented met the criteria which were set out -- safety perhaps; efficacy not even close; equivalence not always close. So, I think the study on its primary endpoint was way under-powered, as was alluded to by the presentation, and the secondary endpoints were mixed. So, despite my interest and enthusiasm, I don't feel I can support it as effective or even equivalent.

DR. WHALEN: I would like to thank everyone who presented today, and especially thank the panel members for

all of their efforts. The meeting is adjourned.

[Whereupon, at 4:40 p.m. the panel adjourned.]

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CERTIFICATE

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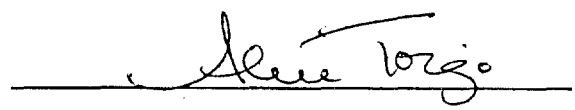

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